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# Part V

## The UNICEF option

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# Part V

## The UNICEF option

### Introduction

UNICEF was established by the United Nations in 1946 to meet the emergency needs of children in post-war Europe and China. In 1950, its mandate was broadened to address the long-term needs of children and mothers in developing countries everywhere. The agency became a permanent part of the United Nations system in 1953.

UNICEF maintains programmes in 161 countries. Some 86% of the organization's 5600 posts are located in the field. There are 8 regional offices and 125 country offices worldwide, as well as a supply operation in Copenhagen, a research centre in Florence and offices in Tokyo and Brussels. UNICEF headquarters is in New York.

UNICEF's activities are directed through an in-country programming process with national counterparts, based on an assessment and analysis of the situation of children and women. The results of this assessment form the basis for the national programme that is submitted to the Executive Board for final approval. This decentralized, country-led process enables UNICEF to tailor its activities to the needs of children in their specific context.

### A. UNICEF Procurement Services

In addition to purchasing for its own country programmes, UNICEF's Supply Division in Copenhagen buys quality supplies at competitive prices on behalf of governments, nongovernmental organizations (NGOs), and UN and development agencies. These procurement services are normally planned as a part of UNICEF collaboration and are complementary to programmes that have been agreed with developing country governments. Priority is given to:

- Essential supplies for the health and development of children and women, particularly essential drugs, micronutrients, medical and educational supplies, and water supply equipment.
- Immunization supplies for the prevention of common diseases in children, including vaccines, injection materials, safety boxes and cold chain equipment.
- Emergency supplies for children, women and families, including blankets, shelter material, impregnated bednets, soap and cooking utensils.
- Special projects consistent with UNICEF programme priorities.

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## 1. *Registration*

In order to access UNICEF procurement services, a prospective customer registers with UNICEF Supply Division as a procurement services customer and signs a Memorandum of Understanding (MOU) that outlines general conditions and the specific responsibilities of UNICEF which will apply to subsequent requests for procurement services. A copy of UNICEF's Standard Purchase Agreement and General Conditions is located at the end of this section as Supplement V.A.1.

**Supplement V.A.1, page 752**

Appropriate agreements are also made between the country field office and the Supply Division in order to clearly establish the roles and responsibilities of each with regard to the MOU. Inquiries about Procurement Services can be made through UNICEF field offices or directly to UNICEF Supply Division in Copenhagen at UNICEF Plads, Freepoort, DK-2100 Copenhagen 0, Denmark, telephone: +45 35 27 35 27; fax: +45 35 26 94 21 or email: customer@unicef.dk.

The UNICEF Supply Division web site at <http://www.supply.unicef.dk/infocustomers.htm> provides general information.

## 2. *Price estimates*

Once registered, the public sector client can indicate type, quantity and delivery date requirements for the products required, and request a price estimate through a local UNICEF representative or by direct enquiry to the Customer Services and Support Centre of the UNICEF Supply Division in Copenhagen. UNICEF will respond with a non-binding estimate, usually within one week, often within two working days.

- Procurement Services customers with Internet access may browse a Product List on the UNICEF web site that includes product specifications and prices, and use a draft order sheet to estimate prices for standard items. (A password is required to view the prices). Contact [psid@unicef.dk](mailto:psid@unicef.dk) for a user ID and password.

## 3. *Orders*

Once the MOU is in place and price estimates have been obtained, customers can place orders through a UNICEF field office or by filling out a Request Form (available on web site to registered purchasers) and submitting it directly to UNICEF Supply Division in Copenhagen. The Supply Division in Copenhagen must approve all procurement services even when programmes are executed entirely by a UNICEF field office.

## 4. *Payment*

UNICEF requires advance payment in US dollars for the full estimated cost of the goods plus handling fees, freight and any applicable contingency amounts (see below), except in a very few acute emergency situations. United States dollars are normally required but UNICEF can sometimes accept payment in local currency within limits defined for each country and approved in advance by UNICEF. These limits are usually tied to the amount of local currency that the UNICEF field office can absorb in its local operations and programmes.

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The required advance payment calculation varies according to the type of item(s) ordered:

1. Warehouse items:
  - Cost of the supplies (ex-warehouse)
  - 6% handling fee (minimum charge US\$ 300)
  - Freight – at cost
  - Insurance – at cost
  - No foreign exchange and market contingency added for items from the warehouse.
  
2. Vaccines:
  - Cost of the supplies
  - 6% handling fee (minimum charge US\$ 300)
  - Freight – at cost
  - Insurance – at cost
  - 10% buffer for market and foreign exchange fluctuations, with the unused portion returned, frequently as credits toward new purchases. The buffer is waived if all parties agree these fluctuations can be reflected in quantities of items supplied.
  
3. Other non-warehouse items:
  - Cost of supplies
  - 8% handling fee (minimum charge US\$ 300)
  - The handling fee will be charged as a percentage of the cost of supplies only
  - Freight – at cost
  - Insurance – at cost
  - 10% buffer for market and foreign exchange fluctuations, with the unused portion returned. The buffer is waived if all parties agree these fluctuations can be reflected in quantities of items supplied.

Unused funds are credited or returned after UNICEF has processed all invoices, including freight bills.

## **B. Vaccine Independence Initiative (VII)**

Introduced in the early 90s, the VII is a planning and financing tool designed to help move developing countries towards sustainable financing of their immunization services.

Under the VII, donors make a one-time contribution on behalf of the client government and UNICEF establishes a revolving fund for the country to use for purchasing vaccine and related goods. The fund acts as a guarantee, so VII countries are not required to pay UNICEF in advance for vaccine purchases. Instead, they replenish the revolving fund after the goods have been received. Currency requirements and limitations are the same for the VII as for standard procurement. An important feature of the VII is that participating governments are encouraged, as part of the process, to make firm and accurate estimates of vaccine requirements, and to place the requirement for vaccines and related supplies into the national health budget.

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## C. Contracts for procurement of vaccines and vaccine related goods

In 1999 UNICEF Supply Division purchased US\$ 101 million in vaccines, US\$ 7 million in syringes and safety boxes and US\$ 4 million in cold chain equipment for its programmes and customers. About 70% of these purchases were for UNICEF-assisted country programmes with the remaining 30% for government immunization services using UNICEF's standard Procurement Services, including the Vaccine Independence Initiative (VII).

### 1. UNICEF procurement of “mature” vaccines

UNICEF subscribes to the principle of competition in the supply of vaccines. It invites WHO-qualified manufacturers to bid for 5-year purchase arrangements (currently for 2001–2005) for OPV and 3-year purchase arrangements (currently for 2001–2003) for other “mature” vaccines (measles–mumps–rubella (MMR), diphtheria–tetanus–pertussis (DTP), diphtheria–tetanus (DT), tetanus toxoid (TT) and BCG), for delivery to all developing countries sourcing and financing vaccines through UNICEF. Multiple awards are made for each product, each award equating to a percentage share of the market covered by UNICEF purchases.

### 2. UNICEF procurement of new and “underused” vaccines

In addition to procurement of “mature” vaccines for the traditional EPI market, UNICEF has committed to purchasing new and “underused” vaccines and related supplies on behalf of the Global Alliance for Vaccines and Immunization (GAVI) for children in the poorest countries in the world. GAVI is described at the end of this Part, in Supplement V.C.2.

Supplement V.C.2, page 758

UNICEF encourages industry to offer significantly discounted prices to the poorest countries market<sup>59</sup> through a process of inviting WHO-qualified manufacturers to provide proposals for 3-year agreements (2001–2003) for immunizing specific numbers of children with “underused” products (hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), yellow fever). UNICEF purchases “underused” vaccines for other countries, if requested, as country-specific markets<sup>60</sup> and commits itself to not considering the prices offered for the poorest countries market as reference prices for country-specific markets.

### 3. Shipping, delivery and distribution

When an order for a basic EPI,<sup>61</sup> “mature” or GAVI-sponsored vaccine is received, UNICEF Supply Division contacts the appropriate manufacturer and the consignment is shipped directly from the manufacturer to the consignee.

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<sup>59</sup> Countries with GNP/capita under US\$ 1000, according to the latest published World Bank statistics, and population under 150 million, according to latest published UN statistics – currently 71 countries.

<sup>60</sup> Each request for supply of “underused” vaccines for a country-specific market requires a separate tender process.

<sup>61</sup> DTP, BCG, OPV, measles.

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UNICEF monitors the vaccine shipments from supplier to arrival at the consignee's designated airport as part of its normal supply service. Delivery is considered to have taken place upon arrival in the country. The "receiving organization in-country" is normally indicated as the consignee on shipments and is expected to clear goods from customs and take on the responsibility of in-country distribution and use. However, UNICEF has a responsibility to monitor distribution and use to ensure that the procurement service objectives are met.

## D. UNICEF vaccine quality programme

The UNICEF Supply Division works closely with WHO in Geneva, and relies on them for product specifications and quality assurance for all vaccine procurement.

### 1. *Pre-qualification*

The Access to Technologies team (ATT) of the Department of Vaccines and Biologicals (V&B) (Health Technology and Pharmaceuticals cluster) at WHO Geneva headquarters acts as an adviser to UNICEF on matters related to the quality of vaccines, and has formulated criteria for evaluating the acceptability of vaccines for purchase by UN agencies. *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/V&B/02.08) is currently being applied to the procurement of vaccines by UNICEF. A model certificate for the release of vaccines acquired by United Nations agencies may be found in Annex 2 of this document.

**Supplement V.D.1, page 761**

### 2. *Quality assurance functions*

WHO also provides quality assurance functions to UNICEF. These functions include random lot testing and follow-up investigation of reported adverse events. In addition, all prequalified suppliers are reassessed on a regular basis. Additional information on vaccine quality assurance measures may be found in Part IV – Quality assurance.

**Part IV, page 669**

### 3. *Specifications*

Specifications for vaccines to be supplied for UNICEF are proposed on advice from WHO. The production characteristics of these products are determined through product-specific guidelines developed by the Expert Committee on Biological Standardization, for which WHO serves as the secretariat. Programmatic specifications are developed based on field need. An example of the requirements for basic vaccines appears at the end of this section in Supplement V.D.3.

**Supplement V.D.3, page 784**

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#### 4. *Application of vaccine vial monitors (WHO specification)*

Vaccine vial monitors are time-temperature sensitive dots that provide an indication on the accumulative heat to which an individual vial has been exposed. They warn the end-user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level. Vaccine vial monitors are now available for all vaccines.

WHO and UNICEF have issued a joint policy statement on the use of vaccine vial monitors in immunization services. This document, *Quality of the cold chain* (WHO/V&B/99.18) Supplement V.D.4 includes the statement: “Agencies purchasing vaccines should request manufacturers to supply all vaccines with vaccine vial monitors (VVMs) that meet WHO specifications”. A copy of the full statement appears at the end of this section. Additional information on vaccine vial monitors is located at VI.H.

**Supplement V.D.4, page 815**

**Part VI.H, page 931**

**UNICEF purchase agreement/general conditions**

PURCHASE AGREEMENT

BETWEEN THE

UNITED NATIONS CHILDREN’S FUND

AND

.....  
.....  
.....

THIS AGREEMENT is entered into between the UNITED NATIONS CHILDREN’S FUND (UNICEF) and

.....

(“Customer”) in accordance with UNICEF Financial Regulation 5.2 and Rules 105.5 to 105.8 to extend to the Customer the facilities and procurement services (“the Services”) provided by the UNICEF Supply Division, whose prime purpose is to purchase and/or stock, set pack (and dispatch) supplies in support of UNICEF programme activities.

WITNESSETH

UNICEF and the Customer hereby agree as follows:

**ARTICLE I**

**Type of services**

1. The Customer recognizes that the Services provided by UNICEF under its Financial Regulations and Rules are limited to assisting governments, UN agencies or other organizations to obtain supplies, equipment and other materials, at a nominal fee, for purpose consistent with the aims and policies of UNICEF.
2. Requests for Services by the Customer may be made for standard warehouse items as listed in the UNICEF Copenhagen Warehouse Catalogue and Price List or non-warehouse items if specifications for such items are clear and complete.
3. Requests for purchases will only be considered by UNICEF where supplies, equipment and services are required for use in projects related to UNICEF programme activities or are consistent with UNICEF’s goals and objectives.
4. UNICEF reserves the right to accept or reject any Request for Services under this Agreement.

## ARTICLE II

### Request for services

1. The Customer shall, for each request for Services under this Agreement, utilize to the extent possible, the same UNICEF forms and follow similar steps to those for UNICEF programme implementation. The request shall be accepted by UNICEF subject to the UNICEF General Conditions.
2. Upon acceptance of the Request, UNICEF will notify the Customer thereof by mailing to the Customer the original of the Request, duly countersigned by an authorized official of UNICEF.
3. Once accepted by UNICEF, the Request and its Annexes shall constitute a contract between UNICEF and the Customer, falling under this Agreement.

## ARTICLE III

### Payment

1. The customer shall, immediately on notification by UNICEF of its acceptance of the Request, deposit an amount covering the total costs of the services in the currency of payment and in the bank account specified by UNICEF.
2. No Request shall be acted upon by UNICEF until the payment due has been made, except where reciprocal arrangements already exist or have been concluded by UNICEF with the Customer with the approval of the UNICEF Comptroller.

## ARTICLE IV

### Terms of delivery

1. All supplies shall be delivered by UNICEF on Cost-Insurance-Freight (CIF) terms, unless otherwise specifically agreed in writing, and the Customer produces proof satisfactory to UNICEF that the shipment will be covered by insurance.
2. UNICEF shall make provision for inspection of purchases prior to shipment and the cost of such inspection, if any, shall be billed to the Customer as part of the cost of the Services provided under the Request.

## ARTICLE V

### Settlement of disputes

1. Any controversy or claim arising out of or in connection with the interpretation or execution of this Agreement or any Request accepted by UNICEF under this Agreement or any breach thereof, shall, unless it is settled by direct negotiations, be settled in accordance with the UNCITRAL Arbitration Rules as at present in force. UNICEF and The Customer agree to be bound by any arbitration award rendered as a result of such arbitration, as the final adjudication of such controversy or claim.
2. Nothing contained in or relating to this Agreement shall be deemed a waiver, express or implied, or any of the privileges and immunities of the United Nations, including UNICEF.

## ARTICLE VI

### Termination

1. The Agreement may be terminated for cause by either Party upon 90 days written notice to the other.
2. Upon termination of this Agreement, the Parties shall take all reasonable and necessary measures to conclude the Services already commenced in accordance with this Agreement.
3. The provisions of this Agreement shall survive any termination to the extent necessary to permit an orderly settlement of accounts between the Parties.

## ARTICLE VII

### General provisions

1. This Agreement shall enter into force upon signature by the Parties.

This Agreement may be altered, modified or amended only by written instrument duly executed by both Parties with the approval of the Comptroller of UNICEF.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement.

on \_\_\_\_\_ at \_\_\_\_\_ on \_\_\_\_\_ at \_\_\_\_\_

*Director, UNICEF Supply Division*

\_\_\_\_\_  
(for the CUSTOMER)

\_\_\_\_\_  
(for UNICEF)

## UNICEF GENERAL CONDITIONS

### Intended purpose

1. The Customer undertakes to ensure that all purchases requested from UNICEF under these arrangements are for purposes consistent with the Purchase Agreement and will be used solely in projects indicated in the Request.

### Cost of purchases

2. Purchases supplied by UNICEF under this Request shall be billed at the price stated by UNICEF. Any price increase resulting from price changes by the Supplier or Manufacturer, currency exchange fluctuations on **non-warehouse items**, or other incidental costs, as may be notified to the Customer, shall be billed and paid by the Customer as part of the total cost of the Services provided by UNICEF.

For **warehouse items** the prices invoiced will be those valid at the time of the receipt and confirmation by Supply Division, Copenhagen of the firm order.

### Payment

3. The Customer shall, as a condition precedent to any action by UNICEF on a Request, pay the amount covering the total cost of the service in a currency and to the bank account agreed. If a price increase is notified to the Customer prior to shipment, the Customer shall immediately arrange for deposit of the amount as provided herein above. If a price increase is notified to the Customer after shipment, the Customer shall pay such price increases within ninety (90) days of such notification.

### Delivery of purchases

4. Delivery of purchases shall be on CIF terms, except where otherwise agreed, upon proof by the Customer that insurance has been effected. The Customer shall be responsible for the purchases from the time of shipment.
5. Upon shipment of the purchases, UNICEF shall forward to the Customer copies of the relevant shipping documents.

### Warranty

6. UNICEF shall pass on any warranty offered by the Manufacturer or Supplier used by UNICEF to the Customer. Where no such warranty is available, UNICEF offers no warranty, express or implied, that supplies are merchantable or fit for any particular purpose. UNICEF will not accept the return of any purchases procured on behalf of the Customer. Only in exceptional circumstances and with the prior agreement of UNICEF may standard warehouse items be returned to UNICEF in Copenhagen, provided that this shall be at the Customer's full expense.

### **Customs clearance**

7. The Customer shall be fully responsible for reception, customs clearance and distribution of all purchases shipped. The Customer or its nominated representative shall be the consignee of such purchases.

### **Amendments, cancellation**

8. Amendments or cancellation or reduction of quantities already accepted by UNICEF, and where procurement action has been initiated, may only be effected with the agreement of UNICEF. The Customer shall be responsible for payment in advance of any resulting costs.
9. In case of cancellation or reduction of quantities before shipment, the customer shall pay any penalties imposed by Suppliers.

### **Final account**

10. After shipment of all purchases and recording of all expenses incurred, UNICEF shall prepare a statement of account to be forwarded to the Customer covering the total cost of the Services, and shall include any increases in cost, including penalties and credits due to decrease in price or quantities.
11. The statement of account shall be expressed in U.S. dollars. The United Nations operational rate of exchange shall apply to all currency conversions under this Request.
12. In the event that the statement of account indicates a balance of funds in favour of the Customer, these funds shall, unless otherwise requested by the Customer, be returned to the Customer.
13. In the event that the statement of account indicates a deficit in the funds deposited with UNICEF, the Customer shall, within ninety (90) days of notification by UNICEF, make the additional payments to the same bank account and in the same currency as the original deposit was made in order to settle the account.

### **Liability and claims**

14. UNICEF shall not be responsible for delay of delivery or loss or damage to any purchases. UNICEF shall under no circumstances be liable for any indirect or consequential damages arising from acceptance or execution by UNICEF of a Request. UNICEF's total liability in any event shall not exceed the purchase price of the particular supply (or supplies) with respect to which a claim is made.
15. All claims relating to any defect in quality or quantity or for any loss or damage shall be handled directly by the Customer with the Supplier. UNICEF shall provide to the Customer any assistance that the Customer may reasonably request in handling such claims.

16. UNICEF accepts no liability for any third party claims arising out of or in connection with the acceptance or execution by UNICEF of the Request. The Customer shall indemnify, deal with, defend and hold UNICEF harmless in connection with any third party claim or other cause of action arising from the acceptance or execution by UNICEF of any Request under the Purchase Agreement.

### **Settlement of disputes**

17. Any controversy or claims arising out of this Request shall be settled as provided in Article V of the Purchase Agreement between UNICEF and the Customer.

## **Global Alliance for Vaccines and Immunization (GAVI)**

The Global Alliance for Vaccines and Immunization (GAVI) was launched in 2000 with the goal of ensuring that every child in the world is protected against vaccine-preventable diseases. The independent GAVI secretariat is housed in the UNICEF offices in Geneva, Switzerland.<sup>46</sup> Its web site is located at <http://www.vaccinealliance.org>.

### *Partnership*

GAVI is a network of international organizations, industrialized and developing countries, technical agencies, research and development agencies, industry, foundations, nongovernmental organizations and other partners involved with immunization in developing countries. GAVI founding partners include:

- Bill and Melinda Gates Children’s Vaccine Program
- International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) and the Developing Country Vaccine Manufacturers Network (DCVMN)
- National governments
- Public health and research institutions
- The Rockefeller Foundation
- United Nations Children’s Fund (UNICEF)
- The World Bank Group
- World Health Organization (WHO)

### *Strategic objectives*

GAVI’s strategic objectives are:

- To improve access to sustainable immunization services
- To expand the use of all existing, safe and cost-effective vaccines where they address a public health priority
- To support the national and international accelerated disease control targets for vaccine-preventable diseases
- To accelerate the development and introduction of new vaccines and technologies
- To accelerate research and development efforts for vaccines intended primarily in developing countries
- To make immunization coverage a centrepiece in international development efforts

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<sup>46</sup> Palais des Nations, CH-1211 Geneva 10, Switzerland; Tel: +41 22 909 5019; Fax: +41 22 909 5931; email: [gavi@unicef.ch](mailto:gavi@unicef.ch).

### *Strategic findings*

Early research by GAVI partners identified two key barriers to universal childhood immunization: insufficient financing and inadequate vaccination infrastructure. GAVI partners developed a financing mechanism to assist in the implementation of its strategic objectives and agreed upon processes from strengthening vaccination infrastructure, focusing particularly on the world's poorest countries. The partners continue to develop mechanisms to support other low and middle income countries.

### **Vaccine Fund**

GAVI partners established a Vaccine Fund and launched it in 2000 with an initial contribution from the Bill & Melinda Gates Foundation of US\$ 750 million over five years. Current resources from the fund are used to help the poorest countries strengthen routine childhood immunization services and introduce new and underused vaccines against HepB, yellow fever and Hib, a major cause of meningitis. One of the overriding concerns of the GAVI partners is to help countries formulate and implement strategies that will sustain improved performance. Recognizing that the lowest income countries will require continued external support for their immunization services, support from the Vaccine Fund has not been envisioned to continue indefinitely but to establish a basis for governments to expand support from other sources.

### *Eligibility for support*

National governments of countries with GNP/capita equal to or below US\$ 1000 are currently eligible for support from the fund. The 74 countries falling into this range have been contacted by GAVI and asked for an indication of their interest.

### *Conditions for support*

The basic conditions for support are:

- a functioning Interagency Coordination Committee (ICC) or equivalent collaboration mechanism;
- an assessment of immunization services during the three last years;
- a multi-year plan for immunization;
- documented efforts to improve the safety of immunization and to plan for sustainable financing of immunization.

### *Applications for support*

Eligible countries must provide the Vaccine Fund with a comprehensive proposal that includes plans for expansion of immunization services and needs for support for new and underused vaccines to be used in their routine childhood immunization system (i.e. EPI.). Vaccines for catch-up and mass immunization campaigns are not provided by the Vaccine Fund.

- Eligible countries with DTP3 coverage below 80% may apply for funding to strengthen their health systems and improve immunization services
- Eligible countries with DTP3 coverage above 50% may apply for support for new and underused vaccines

In the initial phase, vaccines for HepB, Hib and yellow fever will be available from the Vaccine Fund, together with related safe injection equipment. Yellow fever vaccine for routine immunization will also be considered on a country-by-country basis for countries with current DTP3 coverage below 50%.

- All countries receiving an award may also apply for support for auto-disable syringes for all vaccines used in the primary routine immunization services.

# Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies\*

\* This document, produced in March 2002, replaces the previous document WHO/VSQ/97.06



**DEPARTMENT OF VACCINES  
AND BIOLOGICALS**



*World Health Organization*  
**Geneva**  
**2002**

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# Abbreviations

|        |                                              |
|--------|----------------------------------------------|
| ATT    | Access to Technologies team (WHO)            |
| GMP    | good manufacturing practices                 |
| NRA    | national regulatory authority                |
| PAHO   | Pan American Health Organization             |
| PSF    | product summary file                         |
| UN     | United Nations                               |
| UNICEF | United Nations Children’s Fund               |
| V&B    | Department of Vaccines and Biologicals (WHO) |
| VVM    | vaccine vial monitor                         |
| WHO    | World Health Organization                    |

# Introduction

The World Health Organization, through its Department of Vaccines and Biologicals (V&B) provides advice to UNICEF and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies.

The process in place at WHO to assess the acceptability of candidate vaccines for purchase was published initially in the thirty-ninth report of the WHO Expert Committee on Biological Standardization (Technical Report Series 786, Annex 1, 1989). It was further revised and replaced in 1996 by the document *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/VSQ/97.06).

The system in place has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies. In recent years it has been recognized that the system should be expanded to include other vaccines that are or should be used more by countries. This includes vaccines in complex multivalent combinations as well as products used for outbreaks such as cholera and meningitis. It has also been recognized that the system is being used not only by UN agencies, but also by countries looking for guidance on reliable sources of vaccines for purchase.

The present document is a new revision that takes into consideration the above-mentioned considerations, and also includes a new policy governing prequalification of vaccines from manufacturers that perform only bulk filling and formulation activities.

The purpose of the assessment is to verify that the vaccines (a) meet the specifications of the relevant UN agency and (b) are produced and overseen in accord with the principles recommended by WHO, including those for good manufacturing practices (GMP). This is to ensure that vaccines used in national immunization services in different countries are safe and effective and that they meet particular operational specifications for packaging and presentation.

The assessment procedure established by WHO is based on the following principles:

- reliance on the national regulatory authority (NRA) of the country of manufacture;
- general understanding of the product and presentations offered, production process, quality control methods and relevance for the target population of available clinical data;

- assessment of production consistency through compliance with GMP specifications;
- random check-testing of vaccines to monitor compliance with tender specifications on a continuing basis;
- monitoring of complaints from the field.

Since reliance on effective and independent quality assurance by the NRA plays a critical role in the system, WHO recommends that manufacturers (a) inform their NRA of their application for the assessment procedure; (b) at the same time request the NRA to participate in the process; and (c) provide the NRA with the necessary authorization to discuss the relevant files with WHO representatives.

WHO can advise UNICEF and other UN agencies whether vaccines effectively meet WHO-recommended requirements *only if the national regulatory authority of the producing country exercises independent and appropriate oversight of the vaccines in question and if the vaccines have been assessed through the procedure described in this document.*

It should be noted that other vaccines that have not gone through this process may be as safe and effective as those that have actually been assessed.

# Steps of the procedure

WHO requires general information related to the manufacturing company and the product itself. The manufacturer will provide this information through the product file and the site visit. If the manufacturer is not willing to deliver the required information, WHO and the manufacturer will conduct discussions with a view to trying to resolve the situation in a mutually acceptable manner. However, WHO reserves the right to terminate the assessment if at any time it feels that it has not been provided with adequate information to complete the assessment effectively.

## 1. Product summary file

A manufacturer for which the procedure is initiated will provide WHO a request to Coordinator ATT (WHO/V&B) to start the evaluation process and submit a product summary file (PSF) containing information related to the following aspects:

Chapter 1: General information

Chapter 2: Personnel

Chapter 3: Premises and equipment

Chapter 4: Vaccine composition

Chapter 5: Production

Chapter 6: Quality control

Chapter 7: Stability

Chapter 8: Clinical experience

Chapter 9: Production and distribution data

Chapter 10: Update of regulatory authority actions relevant to the product

See **Annex 1** for information on the expected contents of each chapter.

The file will be reviewed by experts in the vaccine(s) in question and by experts in clinical trial evaluation selected and appointed by WHO. During the review of the file, emphasis will be placed on assessing the suitability of the vaccine for the immunization services where it is intended to be used, taking into account composition, presentations offered, recommended schedules and clinical data available, labelling (including vaccine vial monitors), information provided on inserts (which should not contradict WHO model inserts), packaging and shipping procedures in accordance with WHO *International guidelines on packaging and shipping of vaccines* (WHO/V&B/01.05).

The reviewers will provide comments on the acceptability of the information provided and will prepare reports to this effect for WHO. This information will be forwarded to the manufacturers.

## **2. Initial testing of vaccine samples**

The manufacturer will include, with the PSF, summary protocols of no fewer than three lots produced from consecutive bulk lots, and will send separately an appropriate number of samples of each of these final lots to WHO. In some cases, samples of bulk material may be requested. WHO will send the vaccine samples to its collaborating laboratories where they will be tested as appropriate, usually for potency and toxicity. If needed, other tests may be performed.

To promote the independence and objectivity of the testing, the list of WHO's collaborating laboratories will be kept confidential. Neither the manufacturer nor any other party who may have requested that vaccines be tested through this system will be informed where the testing is actually performed. On request, each manufacturer and the relevant NRA will, however, receive a report of the test results.

## **3. NRA evaluation**

As part of this assessment procedure, WHO will ensure that the NRA of the producing country performs the six essential regulatory functions (as established by WHO) with respect to the vaccine or vaccines to be exported through UN agencies.

For this purpose WHO will perform an assessment of the regulatory functions using a set of established indicators (*Regulation of vaccines: building on existing drug regulatory authorities*, WHO/V&B/99.10).

Furthermore, the WHO team will seek an agreement with the NRA for appropriate lot release of all vaccines to be supplied through UN agencies, and sharing of information in case of serious GMP deviations, adverse events following immunization, or withdrawals due to quality issues.

### **. WHO site visits**

When the review of the PSF, testing and regulatory assessment have been satisfactorily completed, WHO will assemble a team to visit the manufacturing facility. UNICEF or the Pan American Health Organization (PAHO) may elect to participate in the team if the vaccine in question is under consideration for supply to these agencies. Otherwise the team will be composed of a group of experts, selected and appointed by WHO, in three main areas: production, quality control and GMP. A WHO representative will lead the team and the team members will act, on a temporary basis, as expert advisers to WHO. The team will perform the site visit and report its findings in accordance with the terms outlined in this document. During the closing meeting at the company, the team will brief the company on the main findings and conclusions and will provide the company with a copy of a draft summary report of the site visit. A full detailed report will be sent by WHO to the company at a later date.

The national regulatory authority will be asked to assign a representative to join the WHO team in their visit to the manufacturing facility to review the manufacturing process, in-process testing, personnel qualifications and practices, animal facilities, compliance with GMP, labelling including vaccine vial monitors (VVMs), packaging and shipping procedures, and post-marketing surveillance activities.

## 5. Report and outcome of the assessment

WHO will write a report of the overall assessment process (including findings, conclusions and recommendations of the site visit) and will send it to the manufacturer with a copy to the NRA.

If minor adjustments need to be made by the manufacturer, WHO will postpone its final recommendations to UNICEF or the other UN agency involved until such adjustments have been incorporated and verified by WHO.

Once WHO considers that the process is complete, and if the outcome is satisfactory, WHO will send a letter to UNICEF or other UN agency involved, advising on (a) compliance of the vaccine with both the requirements recommended by WHO and the specifications of the relevant UN agency, and (b) the role of the NRA in certifying this. This letter will be copied to the manufacturer and the NRA. The vaccine would be then included in the WHO list of pre-qualified vaccines. The current list may be consulted at: <http://www.who.int/vaccines-access/prequalvaccinesproducers.html>. The prequalified status would be valid for a two-year period.

## 6. Special considerations for vaccines formulated and filled by different manufacturers in the same or different countries

There are four basic types of contractual arrangements that may be relevant:

1. *Commodity transaction.* Sale and purchase of bulk vaccine on the open market. Manufacturers and fillers working under this type of arrangement would not be eligible for undergoing the prequalification process for the products in question.
2. *Contract manufacturing.* A contract manufacturer is a facility that is subcontracted by a vaccine manufacturer to do one or more steps of the process. The vaccine manufacturer is responsible for the product and should ensure that all steps of the process are performed in accordance with the licence specifications and in compliance with GMP. A candidate vaccine would be assessed in accordance with the regular procedure as described above.
3. *Partnership/joint venture.* An arrangement between the manufacturer and the finisher, which provides for a stable ongoing supply of bulk to the finisher. This will usually, but not necessarily, include services and mutual monitoring mechanisms as well as the bulk vaccine.
4. *Technology transfer.* Setting up by the manufacturer of a finishing facility, including construction, training of staff, initial activities in assurance of quality and gradual handover to the finisher.

Contractual arrangements of type 3 and 4 above would enable the finisher to undergo the prequalification process, in which case the following criteria would be followed:

1. The assessment evaluation will be product specific just as it is for vaccines produced by one company from seed.
2. The bulk material should be already prequalified by WHO for the UN market under the procedure described above (items 1 to 5).
3. There must be a long-term contract between the bulk manufacturer and the finishing company. The terms of the contract, regardless for which vaccine, should include the criteria described in the document *Guidelines for bulk procurement of oral polio vaccine*, Task Force on Situation Analysis, 29-30 November 1993 (CVI/TFSA/94.4) and should define the liabilities. This contract must be submitted to WHO for review as part of the assessment procedure.
4. The finisher should have authorization from the company producing the bulk to export the final product. A proper assessment of this authorization should be undertaken by the UN purchasing agencies before commitment to purchase. In the case that the bulk antigen A is used for combination with other antigens B and C, proper authorization by the bulk producer of antigen A for combination (and possible limitations for distribution of the combined vaccines) is required, as well as clear demonstration of efficacy and safety of the intended combined vaccine.
5. Each product for which the antigen(s) come(s) from a different manufacturer of bulk is considered as a unique product and will be prequalified separately.
6. The vaccine production process should be overseen by an independent regulatory authority, the options being:
  - a) The national regulatory authority of the country where the bulk is produced (in the case of the bulk), and the national regulatory authority of the finishing country (in the case of the final product). In this option, both authorities must demonstrate to WHO the required technical expertise and the fields of responsibility of each manufacturer, and each NRA must be precisely defined.
  - b) The national regulatory authority of the country where the final product is manufactured oversees the process from seed to finished product. In this case, this authority must demonstrate to WHO the appropriate expertise for this purpose.
7. The product summary file should be submitted to WHO by the finisher, providing details of all the information required in a regular PSF (Annex 1) in relation to the company, general information on bulk material (confidential information is not required), product specifications and detailed information related to all steps to be performed by the finisher.
8. A sample of not fewer than three consecutive lots should be submitted to WHO for independent testing of consistency of final product characteristics (actual number to be decided on a case-by-case basis). Lot summary protocols for these lots should be submitted together with the samples.

9. A full assessment by WHO of the national regulatory authority(ies) that take(s) the responsibility for the oversight of concerned product(s) should take place.
10. A joint technical audit of the finisher's facilities should be carried out by WHO and the regulatory authority that takes responsibility for the oversight of the product.
11. If both the bulk manufacturer and the finisher are seeking prequalification at the same time, technical audits will take place for both the bulk manufacturer and the finisher. In both cases the relevant regulatory authority will be involved.
12. It is desirable, although not imperative, to state on the vaccine box labels the source of the bulk material.
13. The prequalification status will last for a maximum of two years or as long as the contract between the bulk manufacturer and the finishing company remains active.

## 7. Supply

**All lots shipped in response to orders placed by a UN agency must have been released beforehand by the NRA.** Lot-release certificates will be kept by the manufacturer (Annex 2) and sent, on request, to the UNICEF Supply Division or to the Department of Vaccines and Biologicals, Coordinator, Access to Technologies team, World Health Organization, Geneva (WHO/V&B/ATT). In addition, a suitable number of samples of each lot of vaccine supplied will be retained by the manufacturer, to be provided to WHO/V&B/ATT for testing on request.

The manufacturer should inform WHO/V&B/ATT of any changes notified to the NRA in the formulation, in methods of manufacturing, in facilities, or in any other aspects which might (a) result in a change of safety and/or efficacy of the vaccine or (b) change the basis of the regulatory approval by the NRA. Such changes may necessitate a further assessment by WHO to assure continued compliance with WHO-recommended requirements.

## 8. Reassessments

Reassessments will be done in the following situations:

1. At regular intervals, usually every two years.
2. If vaccine fails to meet WHO-recommended requirements and/or the specifications of the offer to bid.
3. If no supply to the UN has taken place for a period equal to, or greater than, two years.
4. In case of a suspension of production.
5. If and when, in the opinion of WHO, changes made in the formulation, manufacturing methods, facilities or other production aspects require that a reassessment be made.

Routine reassessments performed regularly as defined in item (i) above, require:

- Submission of an updated PSF providing information on changes introduced since the previous assessment evaluation (Annex 1).
- Testing of samples.
- Consultation with the NRA on outstanding issues with the vaccine(s) supplied to UN agencies.
- A site visit of the manufacturing facilities, ideally with participation of representatives of the local NRA. The purpose of the visit will be primarily to verify that the vaccine continues to meet WHO-recommended requirements and the specifications of the relevant UN agency, and that it complies with GMP standards. Furthermore, these site visits provide an opportunity for the manufacturer and the team members to discuss any changes which may be foreseen in production and/or quality control methods, as well as any new specifications and/or issues regarding introduction of new policies or strategies proposed by WHO.

The site visit may be waived on a case-by-case basis if the criteria shown in Annex 3 are met. However, a WHO site visit has to take place at a minimum once every five years, regardless of the criteria in Annex 3.

The characteristics of the reassessment will vary depending on the actual circumstances and, for items (ii) to (v) above, may require special provisions, such as submission of specific documents, records, testing of samples and site visit.

## **9. Monitoring of continued compliance with specifications through random testing of samples**

Random samples of lots will be selected, at regular intervals, for independent testing of final product characteristics. On request, each manufacturer and the relevant NRA will receive a report of the test results. Manufacturers will in any case be contacted for follow-up actions in case of failure to meet specifications. Upon request of WHO, the manufacturer or NRA, as appropriate, will provide WHO with lot summary protocols and information on lot release for review.

In the event of failure to meet the established criteria for reassessment or testing, WHO will investigate the problem and provide the UN agency with written information, copied to the manufacturer and the NRA, on the actions that need to be taken.

## **10. Monitoring of complaints from the field**

Complaints from the field concerning vaccines supplied by UNICEF will be communicated via the field officers to the UNICEF Supply Division in Copenhagen. The Supply Division will then request the intervention of WHO to investigate the complaint and ensure that, if necessary, a further in-depth investigation is performed. Complaints communicated by any other route should also be relayed immediately to WHO, through the UNICEF Supply Division in Copenhagen, to allow the investigation procedure to begin.

In the case of vaccines purchased through other UN agencies, the information should be communicated through the relevant purchasing agency to WHO, so that the investigation process can be started.

After investigation, WHO will provide UNICEF or the other UN agency involved with a written report of the problem and include recommendations for action, if any. WHO will then be available as a technical resource while UNICEF or the other UN agency implements the recommendations.

WHO will make a copy of its report available to the manufacturer and the NRA.

## **11. Recommendations for action**

In the event of the situations described in points 9 and 10 above and depending on the nature of the failure to meet the established criteria, WHO may include a recommendation that manufacturers' lots of vaccines are more closely monitored during a probationary period, or that purchase of the vaccine be suspended pending investigation and resolution of the problem, or if a formal reassessment is required, until this has been completed. WHO will generally route communications relating to problems in the field or failure to meet established criteria through the NRA.

## **12. Costs**

The cost of the activities required to assess the acceptability in principle of candidate vaccines for purchase are covered by the manufacturers. The current cost of initial evaluation of a candidate vaccine valid until the year 2004, is US\$ 17 000 (regardless of whether the vaccine is a monovalent or a combined vaccine). The evaluation of a vaccine will be started only after payment of this fee and receipt by WHO of the product summary file. The cost of activities required to keep the WHO list updated (reassessment evaluations) is charged to the manufacturers on the basis of an annual fee which varies according to the antigens contained in the vaccine as shown in table 1:

**Table 1: Annual fee for reassessment purposes  
excluding site visits and extra activities**

| Vaccine group               | Type of vaccine                                                                                                                                                        | Reassessment fee    |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Monovalent vaccines         | Tetanus toxoid, BCG, yellow fever, hepatitis B (HepB), <i>Haemophilus influenzae</i> type b (Hib), measles, rubella, mumps, rabies, meningococcal types A, B or C, etc | Each US\$ 2500/year |
| Two component vaccines      | Diphtheria-tetanus toxoids, measles-rubella combined, meningococcal A+C or B+C, Hib-HepB combined, etc.                                                                | Each US\$ 4000/year |
| Three component vaccines    | Diphtheria-tetanus-pertussis (DTP) combined, measles-mumps-rubella combined, oral polio, inactivated polio (IPV), etc                                                  | Each US\$ 6000/year |
| Four component vaccines     | DTP-Hib combined, DTP-HepB, combined etc                                                                                                                               | Each US\$ 7500/year |
| Five/six component vaccines | DTP-HepB-Hib (fully combined), DTP-IPV, etc                                                                                                                            | Each US\$ 9000/year |

These fees will be valid for an initial period of five years (2000–2004), after which they may be adjusted to reflect increases in the cost of the reassessment process.

The reassessment fees are charged to the manufacturers at the beginning of every calendar year. The reassessment process will not be initiated until the corresponding fees are paid to WHO. Failure to pay could ultimately lead to withdrawal of the vaccines from the list.

Site visits to manufacturing facilities as part of the reassessment process will be waived if certain criteria are met (Annex 3). In all cases where site visits are not waived and in cases where site visits and other additional activities and resources are required for special reasons (e.g. failure to meet the criteria), these will be charged separately on a cost recovery basis.

### 13. Confidentiality

Information to which WHO requires access for the purpose of assessing or reassessing the acceptability in principle of a vaccine for purchase by UN agencies, will not, as a general rule, include confidential information. However, if, in the opinion of the manufacturer, any information to be submitted to WHO and its expert team members in the course of the (re)assessment procedure includes confidential information, the manufacturer must advise WHO thereof in writing, prior to or at the same time as the disclosure, duly identifying the confidential information in question. Notwithstanding the foregoing, WHO and its expert team members will treat all information submitted to them during site visits as confidential, in accordance with the terms set forth below.

WHO will treat information so identified contained in the product summary file (Annex 1) and information disclosed during site visits as confidential and proprietary to the manufacturer and, in this connection, take all reasonable measures to ensure (a) that such information (“the Confidential Information”) is not used for any other purpose than the (re)assessment procedure described in this document, and (b) that it is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO and/or its expert team members will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by the manufacturer; or
- was in the public domain at the time of disclosure by the manufacturer; or
- has become part of the public domain through no fault of WHO and/or any of its expert team members; or
- has become available to WHO and/or any of its expert team members from a third party not in breach of any legal obligations of confidentiality to the manufacturer.

## 1 . No conflict of interest

The team for site visits referred to in point 4 above, includes experts in the field of production, quality control and GMP. These experts are selected by WHO and act as WHO temporary advisers or consultants. Prior to formalizing arrangements with such experts, WHO will require them to complete the WHO declaration of interests form. In addition, the agreement between WHO and such experts will include similar obligations of confidentiality and non-use as contained in point 12 above, as well as a conflict of interest undertaking. Through this conflict of interest undertaking, the aforesaid experts agree to discharge their functions exclusively as advisers to WHO. They also confirm that they have no financial interest and/or other relationship with a party, which:

1. may have a vested commercial interest in obtaining access to any confidential information disclosed by the manufacturer in the course of the (re)assessment procedure described in this document; and/or
2. may have a vested interest in the outcome of the (re)assessment procedure, including, but not limited to, parties such as the manufacturer of the vaccine(s) that is (are) being assessed or manufacturers of competing vaccines.

At the manufacturer’s request, WHO will advise the manufacturer in advance of the composition of the team performing the site visit, and provide *curricula vitae* of the temporary expert advisers included in the team. The manufacturer will then have the opportunity to express possible concerns regarding any of the expert team members to WHO prior to the site visit. If such concerns cannot be resolved in consultation with WHO, the manufacturer may reject an expert team member, within, at the latest, 10 days of receipt of the proposed team composition.

# Annex 1:

## The product summary file

The product summary file (PSF) is a brief (1-2 volume) summary dossier containing current information on the product to be supplied to UN agencies. It presents information on the product composition, manufacturing procedure, testing, clinical experience, and available post-marketing safety information.

For initial product *assessments*, a product summary file should be submitted for each vaccine to be assessed. For combination vaccines, information should be submitted on each of the component vaccines and on the combination itself.

The product summary file is expected to contain the following elements:

### Chapter 1: General information

- 1.1 Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understanding the manufacturing process. Name and address of the site, including telephone, fax and 24-hour telephone numbers.
- 1.2 Pharmaceutical and non-pharmaceutical manufacturing activities carried out on the site as licensed by the national regulatory authority.
- 1.3 Short description of the site (size, location and immediate environment and other manufacturing activities on the site).
- 1.4 Number of employees engaged in the production, quality control, storage and distribution.
- 1.5 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis. In case of contract manufacturing of part of the process, information on the way in which GMP compliance of the contract acceptor is assessed.
- 1.6 Short description of the quality management system of the firm responsible for manufacture.
- 1.7 Short description of the internal audit system.

### Chapter 2: Personnel

- 2.1 Organizational chart showing the relationships between different areas including quality assurance, production and quality control, with identification by name of key personnel.
- 2.2 Qualifications, experience and responsibilities of key personnel.

- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
- 2.4 Health requirements for personnel engaged in production, particularly relating to requirements for immune status for production personnel.

### **Chapter 3: Premises and equipment**

These will be examined in depth during the site visit. However, the following preliminary information should be submitted:

- 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawing are not required).
- 3.2 Nature of construction and finishes.
- 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the clean-rooms used for the manufacture of sterile products should be included.
- 3.4 Special areas for the handling of highly toxic, hazardous and sensitizing materials.
- 3.5 Brief description of water systems (schematic drawings of the systems are desirable) including sanitation.
- 3.6 Maintenance (description of planned preventive maintenance programmes and recording system).
- 3.7 Brief description of major production and control laboratories equipment (a list is not required).
- 3.8 For products where separate facility is required (e.g. tetanus, BCG) describe how separation is achieved. For multipurpose areas, describe cleaning system between campaigns.
- 3.9 Description of qualification and validation procedures, including computerized recording and controller systems.
- 3.10 Availability of written specification and procedures for cleaning manufacturing areas and equipment.

### **Chapter : Vaccine composition, presentations and schedules**

- 4.1 Formulation of the product.
- 4.2 Brief description of the presentations made available to UN agencies, including diluent (if applicable), combination products, forms, dose sizes, type of containers, VVM type used and descriptions of application devices (e.g. syringes) to be delivered with the vaccine, if applicable.
- 4.3 Recommended schedule and route of administration.
- 4.4 Samples of labels, boxes and package inserts to be used for UN agencies' supply. Samples of vials or ampoules of diluent and its corresponding labelling.
- 4.5 Sample of lot summary protocol to be provided to UN agencies (to follow the WHO-recommended format).

## **Chapter 5: Production\***

- 5.1 Manufacturing formula (including details of batch size).
- 5.2 Description of the manufacturing processes and the characterization of the product together with a flow-chart showing the control tests performed on intermediate and final products and an identification of any processes or tests performed by contract manufacturers or testers. For recombinant vaccines, a description of the construction and characterization of the recombinant vector should be provided.
- 5.3 Brief description of general policy for process validation. List of the process validation activities performed.
- 5.4 Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
- 5.5 Arrangements for the handling and procedures for destruction of rejected materials and products.

## **Chapter 6: Quality control\***

- 6.1 Starting materials.
  - 6.1.1 Control tests performed on raw materials, with appropriate characterization of starting materials.
  - 6.1.2 Control tests performed on labelling and packaging material(s).
- 6.2 Intermediate products (as appropriate).
  - 6.2.1 Specifications and routine tests performed.
  - 6.2.2 List of test validation activities performed.
- 6.3 Finished products.
  - 6.3.1 Specifications and routine tests performed.
  - 6.3.2 List of test validation activities performed.

## **Chapter 7: Stability**

- 7.1 Stability tests on intermediates, assigned shelf life and storage conditions.
- 7.2 Stability tests on the finished product, assigned shelf life and storage conditions.
- 7.3 Description of the policy for assigning the date of manufacture of each component as well as the final product (e.g. combination vaccine) and diluents, as appropriate.

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\* WHO recommended requirements or guidelines and UN agency tender specifications must be met. For each specific test done, the international standard met should be identified.

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## **Chapter 8: Clinical experience**

- 8.1 Clinical trial results to show the safety and efficacy of the vaccine in the target population, at the dosage and schedules intended to be used in national immunization services. This data has to be relevant to the developing country public sector target population at the recommended schedules.
- 8.2 Published reports in scientific and medical literature summarizing efficacy or safety studies (other than 8.1).
- 8.3 Additional reports of clinical experience or toxicity studies pertinent to safety (for example, epidemiological studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the manufacturer.
- 8.4 Summary of available post-marketing reporting of adverse events.

## **Chapter 9: Production and distribution data**

- 9.1 The quantity of finished product distributed domestically and exported in the previous three years.
- 9.2 Arrangements and recording system for distribution.
- 9.3 Arrangements for the handling of complaints and product recalls (only for reassessment purposes).
- 9.4 The quantity of finished product (differentiating combination products) supplied to UN agencies on a per annum basis.
- 9.5 The quantity of bulk vaccine destined for UN agencies, supplied to contract fillers/packagegers for finalization (list individually).

## **Chapter 10: Update of regulatory authority actions relevant to the product**

- 10.1 Copy of marketing authorizations, information on refusals, withdrawals, or suspensions including those that are manufacturer initiated.
- 10.2 Restrictions on distribution or recalls, including manufacturer-initiated recalls.
- 10.3 Clinical trial suspensions, including manufacturer-initiated suspensions.
- 10.4 Dosage or schedule modifications.
- 10.5 Changes in target populations or indications.
- 10.6 Reports of inspections conducted by national authorities within the previous two years.
- 10.7 Inspections conducted by foreign authorities within the previous two years.

# Annex 2:

## Model certificate for the release of vaccines acquired by UN agencies

(Revised 1988)

**(To be completed by the national control authority of the country where the vaccines have been manufactured, and to be sent by the vaccine manufacturer to UNICEF.)**

The following lots of .....<sup>1</sup> vaccine produced by .....<sup>2</sup> in .....<sup>3</sup>, whose numbers appear on the labels of the final containers, meet all national requirements.<sup>4</sup> Part A<sup>5</sup> of Requirements for Biological Substances No. ....<sup>6</sup> (Requirements for .....<sup>1</sup>, published in 19..... [if applicable, revised 19....., addendum 19.....]) and Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, published in 1959; revised 19.....).<sup>7</sup>

| Lot No. | Expiry date | Lot No. | Expiry date |
|---------|-------------|---------|-------------|
| .....   | .....       | .....   | .....       |
| .....   | .....       | .....   | .....       |
| .....   | .....       | .....   | .....       |
| .....   | .....       | .....   | .....       |

As a minimum, this certificate is based on examination of the manufacturing protocol. The Director of the National Control Laboratory (or Authority as appropriate)<sup>8</sup>

Name (typed) .....

Signature .....

Date .....

<sup>1</sup> Indicate type of vaccine (measles, oral poliomyelitis, tetanus, diphtheria-tetanus, diphtheria-pertussis-tetanus, BCG).  
<sup>2</sup> Name of manufacturer.  
<sup>3</sup> Country.  
<sup>4</sup> If any national requirements are not met, specify which one(s) and indicate why release of the lot(s) has nevertheless been authorized by the national control authority.  
<sup>5</sup> With the exception of the provisions on shipping, which the national control authority may not be in a position to control.  
<sup>6</sup> Indicate the reference number of the relevant Requirements for Biological Substances published by WHO.  
<sup>7</sup> These requirements were revised in 1965; a further revision is in preparation for consideration by the WHO Expert Committee on Biological Standardization in 1989.  
<sup>8</sup> Or his or her representative.

# Annex 3:

## Criteria for waiving a site visit during the WHO re-assessment procedure for vaccines supplied to UN agencies

*All* the following criteria should be met.

1. A GMP inspection relevant to the product(s) has been conducted within the previous five years, by a competent authority, either national or foreign, and a copy of the inspection report in English has been made available to WHO.
2. A site visit has been conducted by WHO within the last five years.
3. There have been no significant changes or additions to the approved processes and procedures listed in the national authorization of the manufacturing and testing facilities.
4. There have been no significant changes in the product indications, patient groups, or consumer warnings as compared to those mentioned in the regulatory approval of the country of manufacture.
5. There have been no recalls of the product(s) and there have been no withdrawals or cancellations of registration licences related to quality issues since the previous reassessment evaluation.
6. Significant changes to the product or its manufacturing processes or facilities (which can potentially have effects on the product's quality, safety or efficacy) have been notified to WHO (with adequate information to justify the change), before the changed product has been supplied to UN Agencies, *and* WHO has not found that these changes require a reassessment with a site visit.
7. No confirmed incidents related to non-compliance with quality specifications of tenders have been received by WHO with regard to the product(s) since the previous reassessment evaluation.
8. No significant complaints from the field or reports of adverse events following immunization (AEFI) attributable to quality of the product(s) have been received and confirmed by WHO.
9. Post-market surveillance or studies conducted by or otherwise obtained by the manufacturer or the national regulatory authority in regard of the product(s) have shown no significant increase in expected or unexpected adverse events in an established or new patient group.
10. It is assured that the national regulatory authority will continue to function well through open and timely communication with WHO on issues of vaccine quality impacting the UN market (e.g. changes to the license, reports of AEFI, withdrawals, changes in indications, major GMP non-compliance, etc.).

## Annex 4:

### Provisions for team members participating in WHO missions to assess acceptability, in principle, of vaccines for purchase by UN agencies

In the course of discharging your functions as an expert adviser under this Agreement, you will gain access to certain information, which is proprietary to WHO or to the manufacturer(s) of the vaccine(s) which need(s) to be assessed for purchase by UN agencies. You undertake to treat such information (hereinafter referred to as “the Information”) as confidential and proprietary to WHO or the aforesaid manufacturer(s). In this connection, you agree to:

1. not use the Information for any other purpose than discharging your obligations under this Agreement; and
2. not disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

However, you will not be bound by any obligations of confidentiality and non-use to the extent that you are clearly able to demonstrate that any part of the Information:

1. was known to you prior to any disclosure by WHO and/or the manufacturer(s); or
2. was in the public domain at the time of disclosure by WHO and/or the manufacturer(s); or
3. has become part of the public domain through no fault of your own; or
4. has become available to you from a third party not in breach of any legal obligations of confidentiality to WHO and/or the manufacturer(s).

You also undertake not to communicate the deliberations and findings of the team(s) of experts in which you will participate, as well as any resulting recommendations and/or decisions of WHO, to any third party, except as explicitly agreed by WHO.

You will discharge your responsibilities hereunder exclusively in your capacity as an expert adviser to WHO. By signing this Agreement, you furthermore confirm that you have no financial interest and/or other relationship with a party, which:

1. may have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or
2. may have a vested interest in the outcome of the assessment of the vaccine(s), in which you will participate, including but not limited to parties, such as the manufacturer(s) of the vaccine(s) that is (are) being assessed or manufacturers of competing vaccines.

In this regard, it should be noted that the manufacturer(s) of the vaccine(s) under evaluation have the right to object to your participation in the team(s) of experts which will evaluate (its) (their) vaccine(s). If such objection cannot be resolved in consultation with the manufacturer(s), WHO shall be entitled to terminate this Agreement or cancel part of the activities to be undertaken by you hereunder. The travel and per diem allowances payable to you under this Agreement will in such event be adjusted accordingly.

I hereby agree to the conditions and provisions contained in this document.

**Signed:** .....

**Name (typewritten):** .....

**Institute:** .....

**Place:** .....

**Date:** .....

## **D. Minimum requirements for vaccines to be procured by UNICEF**

### **8.1 Production and testing**

The vaccines shall be produced and tested in conformity with the requirements of national legislation and the following requirements established by the World Health Organization (WHO).

- 8.1.1 *Good manufacturing practices for biological products* (WHO Technical Report Series No. 822, 1992) and *Guideline for national authorities on quality assurance for biological products* (WHO Technical Report Series No. 822, 1992).
- 8.1.2 *Good manufacturing practices for pharmaceutical manufacturers* (WHO Technical Report Series No. 823, 1992).
- 8.1.3 *Guide for inspection of manufacturers of biological products* (WHO/VSQ/97.03).
- 8.1.4 *General requirements for the sterility of biological substances* (WHO Technical Report Series No. 530, 1973), Amendment 1995 (WHO Technical Report Series No. 872, 1998).
- 8.1.5 *Requirements for the use of animal cells as in vitro substrates for the production of biologicals* (WHO Technical Report Series No. 878, 1998).
- 8.1.6 *Report of a WHO Consultation on Medicinal and other Products in relation to Human and Animal Transmissible Spongiform Encephalopathies* (WHO/BLG/97.2).

### **8.2 Vaccines**

- 8.2.1 *Requirements for measles, mumps and rubella vaccines and combined vaccines (live)*. (WHO Technical Report Series No. 840, 1994).
- 8.2.2 *Requirements for hepatitis B vaccine made by recombinant DNA techniques* (WHO Technical Report Series No. 786, 1989).
- 8.2.3 *Requirements for hepatitis B vaccine prepared from plasma*. Revised 1987 (WHO Technical Report Series No. 771, 1988).
- 8.2.4 *Requirements for Meningococcal Polysaccharide Vaccine* (WHO Technical Report Series No. 574, 1976) Addendum 1980 (WHO Technical Report Series No. 658, 1981).
- 8.2.5 *Requirements for poliomyelitis vaccine (Oral)* (Revised 1999) (WHO Technical Report Series No. 904, 1999) except that the minimum infectious units per human dose for type 3 should be 600 000. This is specified by WHO-EPI following the recommendation of the Global Advisory Group of its meeting in Cairo 1990. An addendum, which includes several additional recommendations, was adopted by the Expert Committee on Biological Standardization (ECBS) in 1998, and will appear in the Technical Report Series, WHO ECBS 49<sup>th</sup> Report.
- 8.2.6 *Requirements for yellow fever vaccine* (WHO Technical Report Series No. 872, 1998).

- 8.2.7 *Revised requirements for dried BCG vaccine* (Revised 1985) (WHO Technical Report Series No. 745, 1987), Amendment 1987 (WHO Technical Report Series No. 771, 1988).
- 8.2.8 *Requirements for diphtheria, tetanus, pertussis and combined vaccines* (Revised 1989) (WHO Technical Report Series No. 800, 1990).
- 8.2.9 *Requirements for Haemophilus influenzae type B conjugate vaccine* (WHO Technical Report Series No. 897, 2000).
- 8.2.10 If there is a change in formulation of vaccines from those supplied to UNICEF in 2001 against previous long term arrangements, manufacturing protocols plus data on thermostability where appropriate and final container samples from five consecutive bulk lots shall be provided through the national regulatory authority to the Coordinator, Access to Technologies/V&B/WHO Geneva before the bid is considered.
- 8.2.11 Regarding BCG vaccine, freeze-dried, nominal 10 and 20 dose vials should contain actual 10 and 20 doses respectively for children under one year old, i.e. reconstituted vaccine of 0.5 ml and 1.0 ml respectively (0.05 ml/dose x 10 and 20 doses respectively) as described in page 14, BCG vaccine model insert. Therefore, any supplier's nominal vials that do not fulfil the above requirement may either be rejected or the offer adjusted to equivalent vial sizes.
- 8.2.12 It is recognized that, because of the special needs for vaccines for national immunization services in developing countries, the specifications prepared for UNICEF by WHO may be more detailed than those given in the WHO requirements, although they are not in conflict with them. If these specifications are not in accord with national requirements, provision is made for this to be stated in the model certificate for the release of vaccines acquired by United Nations agencies (TRS 786, Annex 1, Appendix 2).

### 8.3 *Shelflife*

Vaccine shall be supplied with the maximum shelf life possible consistent with current vaccine production technology. Unless separately authorized by UNICEF, the remaining shelf life at the time of dispatch shall not be less than the figures given below:

|                                                        |           |
|--------------------------------------------------------|-----------|
| Oral polio vaccine, if stored at -20°C                 | 18 months |
| Freeze-dried BCG, freeze-dried measles, DTP, TT and DT | 20 months |

### 8.4 *Packing and shipping*

Packing/shipping requirements must conform to the attached *WHO guidelines on the international packaging and shipping of vaccines* (WHO/V&B/01.05).

## 8.5 *Labels and inserts*

- 8.5.1 Vial labels shall be affixed with water resistant adhesive so that the labels do not become loose or fall off. Labels shall state the name of vaccine, name of manufacturer, place of manufacture, lot number, composition, concentration, dose and mode of administration, expiry date, storage temperature and any marking that is appropriate. Expiry date and lot number shall be printed on each vial in indelible ink.
- 8.5.2 Inserts shall be printed in English, French, Portuguese and Russian (Spanish and Arabic are optional). Separate inserts in the language appropriate for the country of destination will be welcome. In all inserts the following should be inserted under “Description of vaccines”.
- “The vaccine fulfils WHO requirements for \_\_\_\_\_  
(name of vaccine)”.
- 8.5.3 Inserts shall contain at least the information in the WHO Model Insert enclosed for that vaccine. Any additional information provided by the manufacturer must not confuse or contradict WHO policy on the use of that vaccine. It should also be noted that current model inserts attached will be revised and replaced during this year.

## 8.6 *Closures*

Vaccine vials shall be fitted with closures that conform to ISO standards 8362-1 and 8362-2.

## 8.7 *Vaccine vial monitors (VVMs)*

VVMs should comply with WHO technical specifications E6/IN5 dated 25 March 2002 or later.

## 8.8 *Model Inserts*

### BCG vaccine

#### Description

It is a live freeze-dried vaccine made from an attenuated strain of *Mycobacterium bovis*. It is used for the prevention of tuberculosis. It contains..... (specify) as a stabilizer.

#### Administration

For children under one year 0.05 ml, and for others 0.1 ml of reconstituted vaccine is given **intradermally**. Special syringes allow administration of the exact dose. A sterile syringe and a sterile needle should be used for each injection. The skin should not be cleaned with antiseptic. Special care is needed in opening the vial so that the vaccine is not blown out. Because of sensitivity to ultraviolet light, the vaccine must be protected from sunlight. If not used immediately after reconstitution, the vaccine should be kept on ice to maintain its temperature between +2°C and +8°C. Any opened container remaining at the end of a session (within six hours of reconstitution) must be discarded.

The diluent supplied is specially designed for use with this vaccine. Only this diluent may be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or from other manufacturers. Water for injection may **not** be used for this purpose. **Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine.** Diluent must not be frozen but must be cooled between +2°C and +8°C before reconstitution. If the vaccine vial monitor (see figure) is present, it is removed on reconstitution.

Skin testing with tuberculin is not generally carried out before giving BCG, but when performed, those who are found to be positive reactors need not be immunized.

#### Immunization schedule

BCG should be given routinely to all infants at risk of early exposure to the disease. For maximum protection, this vaccine should be given as soon after birth as possible. It can be given at the same time as DTP, measles, polio (OPV and IPV), hepatitis B, *Haemophilus influenzae* type b, and yellow fever vaccines and vitamin A supplementation.

#### Side effects

A local reaction is normal after BCG. A small tender red swelling appears at the site of the injection, which gradually changes to a small vesicle and then an ulcer in 2–4 weeks. The reaction usually subsides within two to five months and in practically all children leaves a superficial scar 2–10 mm in diameter. Rarely, the nodule may persist and ulcerate. Occasionally, enlargement of axillary lymph nodes may appear in 2–4 months following immunization. Very rarely, enlarged lymph nodes can suppurate. Inadvertent subcutaneous injection may produce abscess formation and may lead to scarring.

## Contraindications

Keloid and lupoid reactions may also occur at the site of injection and children experiencing such reactions should not be revaccinated.

Do not give in pregnancy.

## Immune deficiency

Non-symptomatic individuals infected with human immunodeficiency virus (HIV) should be immunized with BCG vaccine according to standard schedules. The vaccine is contraindicated in individuals with cell-mediated immune deficiency. **Individuals with clinical (symptomatic) AIDS should NOT receive BCG vaccine.**

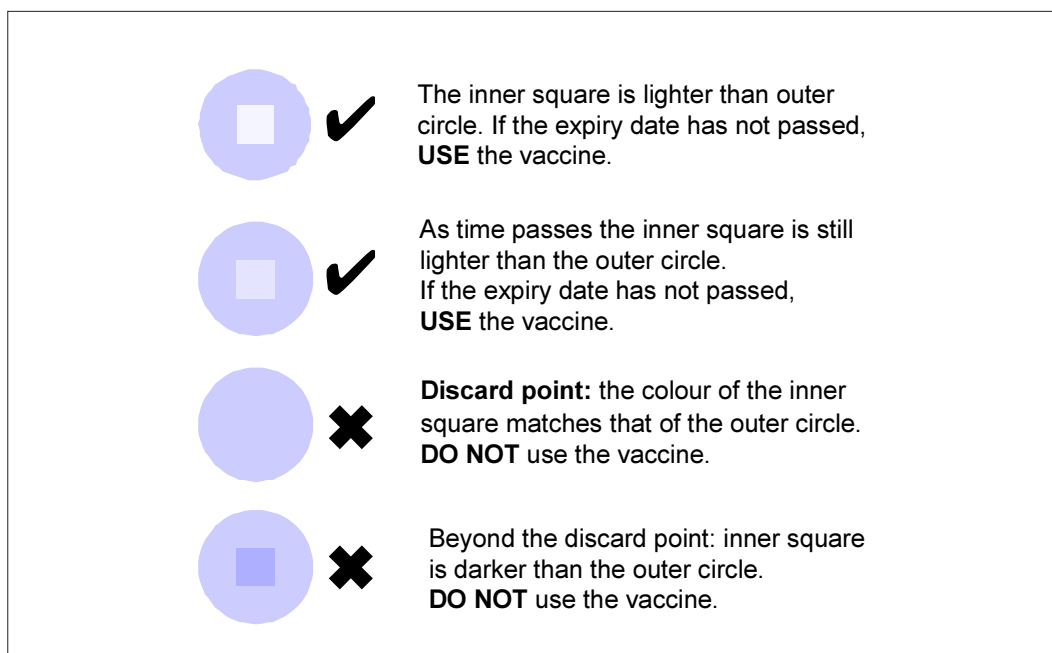
## Storage

BCG vaccine should be stored and transported between +2°C and +8°C. It is even more stable if stored in temperatures as low as -20°C. The diluent should not be frozen. The vaccine should be protected from the light. Vaccine vials and diluents should be transported together.

## Presentation

The vaccine comes in boxes of ..... (specify) ampoules/vials each containing ..... (specify) doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot, which appears on the label of the vial, is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## DTP vaccine

### Description

The vaccine contains purified diphtheria and tetanus toxoids and inactivated whooping cough organisms. The vaccine is adsorbed onto ..... (specify). ..... (specify) is used as a preservative (specify amount per dose). The potency of the vaccine per single human dose is at least 4 IU (international units) for pertussis, 30 IU for diphtheria and for tetanus 60 IU (determined in mice) or 40 IU (determined in guinea pig).

### Administration

The vaccine vial should be shaken to homogenize the suspension. The vaccine should be injected intramuscularly or deep subcutaneously. The anterolateral aspect of the upper thigh is the preferred site of injection. (An injection into a child's buttocks may cause injury to the sciatic nerve and is not recommended.) It must not be injected into the skin as this may give rise to local reaction. One dose is 0.5 ml. A sterile needle and sterile syringe should be used for each injection.

Once opened, multi-dose vials should be kept between +2°C and +8°C.

Multi-dose vials of DTP from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the *WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water;
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point. (see figure).

### Immunization schedule

In countries where pertussis is of particular danger to young infants, DTP immunization should be started as soon as possible with the first dose given as early as 6 weeks, and two subsequent doses given at 4-week intervals.

DTP vaccine can be given safely and effectively at the same time as BCG, measles and polio vaccines (OPV and IPV), hepatitis B, *Haemophilus influenzae* type b, yellow fever vaccine and vitamin A supplementation. WHO recommends that, where resources permit, an additional dose of DTP be given approximately one year after completion of the primary doses. However, the need for additional booster doses of DTP, DT or Td should be addressed by individual national immunization programmes. DTP vaccine can be given safely at the same time as other vaccines according to national immunization schedules.

## Side effects

Mild local or systemic reactions are common. Some temporary swelling, tenderness and redness at the site of injection together with fever occur in a large proportion of cases. Occasionally severe reactions of high fever, irritability and screaming develop within 24 hours of administration. Hypotonic-hyporesponsive episodes have been reported. Febrile convulsions have been reported at a rate of one per 12 500 doses administered. Administration of acetaminophen at the time of and 4–8 hours after immunization decreases the subsequent incidence of febrile reactions. The national childhood encephalopathy study in the United Kingdom showed a small increased risk of acute encephalopathy (primarily seizures) following DTP immunization. However subsequent detailed reviews of all available studies by a number of groups, including the United States Institute of Medicine, the Advisory Committee on Immunization Practices, and the paediatric associations of Australia, Canada, the United Kingdom and the United States, concluded that the data did not demonstrate a causal relationship between DTwP and chronic nervous system dysfunction in children. Thus there is no scientific evidence that hypotonic-hyporesponsive episode and febrile convulsions have any permanent consequences for the children.\*

## Contraindications

DTP vaccine should not be given to individuals who had an anaphylactic reaction to a previous dose or to any constituent of the vaccine.

## Immune deficiency

Individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with DTP vaccine according to standard schedules.

## Storage

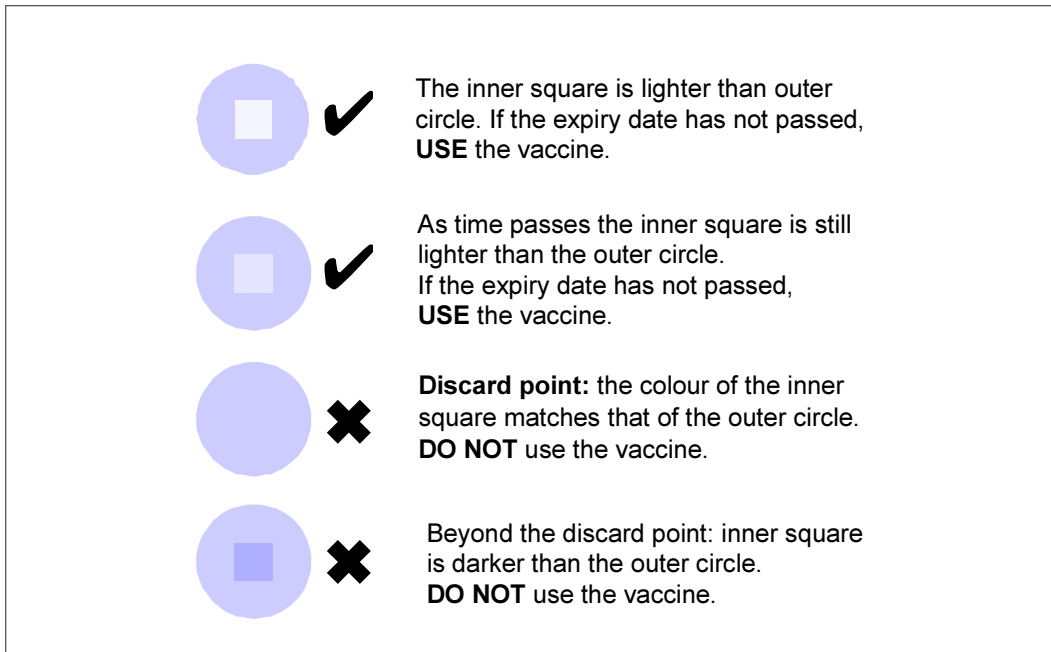
DTP vaccine should be stored and transported between +2°C and +8°C. **It must not be frozen.**

## Presentation

The vaccine comes in vials of ..... (specify) doses.

\* *In Weekly Epidemiological Record*, No. 18, 7 May 1999. Page 139

**Figure: The vaccine vial monitor**



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## TT vaccine

### Description

The vaccine contains purified tetanus toxoid. The toxoid is adsorbed onto ..... (specify). ..... (specify) is used as a preservative (specify amount per dose). One dose of 0.5 ml has a potency of at least 40 IU.

### Administration

The vaccine vial should be shaken before use to homogenize the suspension. It should be injected intramuscularly. A sterile needle and a sterile syringe should be used for each injection.

Once opened, multi-dose vials should be kept between +2°C and +8°C. **Multi-dose vials of TT from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of weeks**, provided that all of the following conditions are met (as described in the *WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure).

### Immunization schedule

TT immunization for the prevention of tetanus/neonatal tetanus consists of two primary doses of 0.5 ml given intramuscularly at least four weeks apart followed by the third dose at least 6 months later. To maintain the immunity of women against tetanus through the child-bearing period, a total of five doses are recommended. A fourth dose should be given at least one year after the third dose, and a fifth dose at least one year after the fourth dose. TT immunization can be administered safely during pregnancy even during the first trimester. In previously non-immunized women, two doses of TT are recommended in pregnancy, at least 4 weeks apart, the second dose should be given at least two weeks before childbirth, in order to prevent maternal and neonatal tetanus.

TT may be given at the same time as BCG, measles, rubella, mumps, polio (OPV and IPV), hepatitis B, *Haemophilus influenzae* type b, and yellow fever vaccines and vitamin A supplementation.

### Side effects

Rare and mild. Some temporary tenderness and redness at the site of the injection and occasional fever. It is safe to be given during pregnancy.

## Contraindications

A severe reaction to a previous dose of TT.

## Immune deficiency

Persons infected with human immunodeficiency virus (HIV) whether asymptomatic or symptomatic, should be immunized with TT vaccine according to standard schedules.

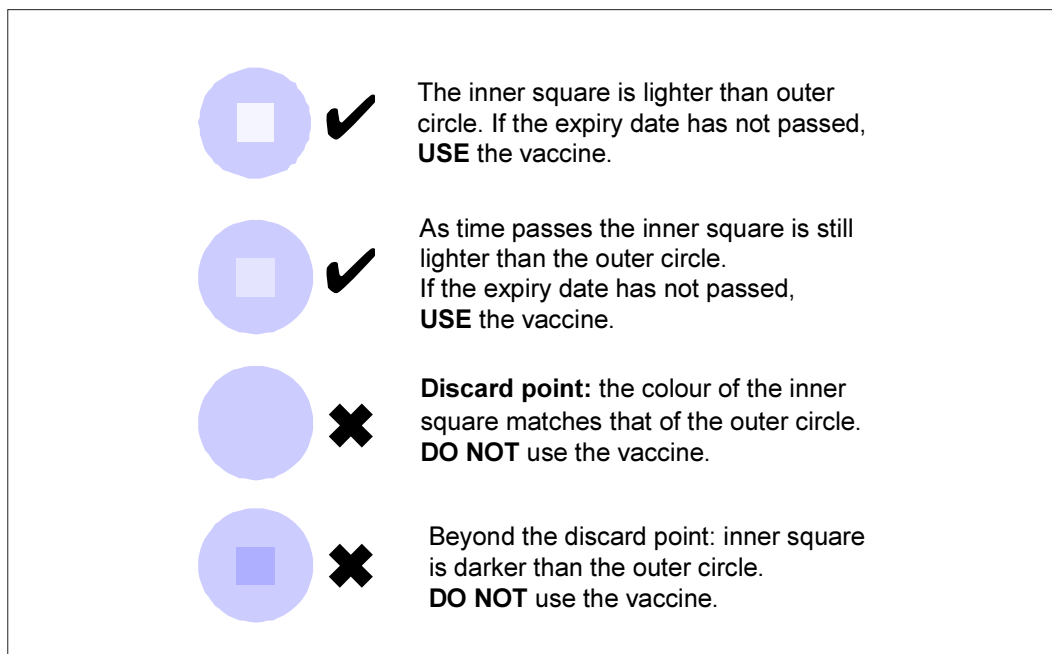
## Storage

TT should be stored and transported between +2°C and +8°C. **It must not be frozen.**

## Presentation

The vaccine comes in vials of ..... doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## Adsorbed DT vaccine for children

### Description

The vaccine contains purified diphtheria and tetanus toxoids. The toxoids are adsorbed onto ..... (specify). ..... (specify) is used as a preservative (specify amount per dose). The potency of vaccine components per single human dose is at least 30 IU of potency for diphtheria toxoid and at least 40 IU of potency for tetanus toxoid.

### Administration

The vaccine vial should be shaken before use to homogenize the suspension. The vaccine should be injected intramuscularly. A sterile syringe and a sterile needle should be used for each injection. DT vaccine is recommended for children below 7 years of age. For persons 7 years and older, a special adsorbed vaccine for adults, Td, is recommended.

Once opened, multi-dose vials should be kept between +2°C and +8°C. Multi-dose vials of DT from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the *WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure).

### Immunization schedule

Recommended for use in childhood immunization instead of DTP when contraindications to pertussis component exist. Three intramuscular injections of 0.5 ml at least four weeks apart provide primary immunization for children. DT may be given at the same time as BCG, measles, rubella, mumps, polio vaccines (OPV and IPV), hepatitis B, Hib, yellow fever vaccine and vitamin A supplementation.

### Side effects

Some temporary tenderness and redness at the site of the injection and occasional fever may occur.

### Contraindications

A second or subsequent dose of DT should not be given to a child who suffered a severe reaction to the previous dose.

## Immune deficiency

Individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with DT vaccine according to standard schedules.

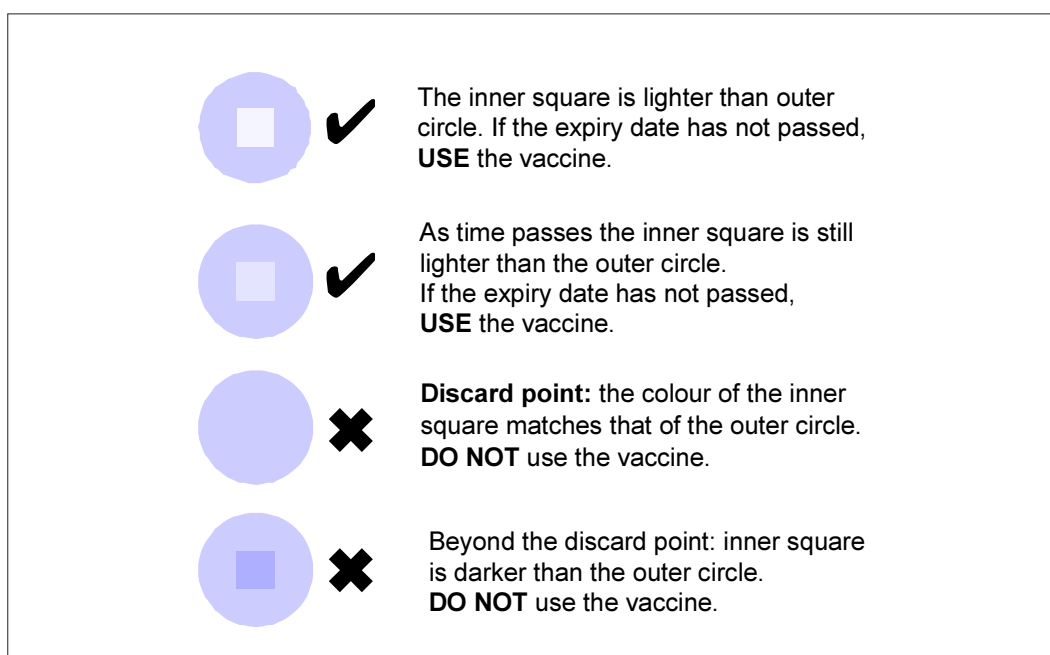
## Storage

DT should be stored and transported between +2°C and +8°C. **It must not be frozen.**

## Presentation

The vaccine comes in vials of ..... (specify) doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## Measles vaccine

### Description

It is an attenuated live virus vaccine. Each dose contains not less than..... (specify) CCID<sub>50</sub> (cell culture infective doses 50%) of viral vaccine strain..... (specify), prepared in ..... (specify substrate) and not more than ..... mgm of residual antibiotic (specify..... ). This vaccine is a freeze-dried product that must be reconstituted only with the sterile diluent provided separately for that purpose.

### Administration

Immunization consists of a single dose of 0.5 ml injected percutaneously (subcutaneous or intra-muscular), preferably in the upper arm. A sterile needle and sterile syringe must be used for each injection. Because of sensitivity to ultraviolet light, avoid exposing the vaccine to sunlight. Once the vaccine has been reconstituted, it should be used the same day (preferably immediately but by no means beyond six (6) hours after reconstitution), and only then if the vial has been maintained between +2°C and +8°C and protected from sunlight. Any opened container remaining at the end of a session (within six hours of reconstitution) should be discarded. The vaccine vial monitor (see figure), if present, would have been removed on reconstitution.

The diluent supplied is specially designed for use with this vaccine. Only this diluent may be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or for measles vaccine from other manufacturers. Water for injection may **not** be used for this purpose. **Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine.** Diluent must not be frozen but must be cooled between +2°C and +8°C before reconstitution.

### Immunization schedule

In countries where the incidence and mortality from measles is high in the first year of life, the recommended age for immunization against measles is at 9 months of age (270 days) or shortly after. In countries where infection occurs later in life (due to sustained high vaccine coverage), the age of immunization can be moved to 12–15 months. A second opportunity is needed both to increase the chance that every child receives at least one dose of measles vaccine and to increase the proportion of the population that is fully immunized. The second dose can be given at least one month after the first dose through routine or supplemental activities. Measles vaccine can be given safely and effectively simultaneously with DTP, Td, TT, BCG, polio (OPV and IPV), *Haemophilus influenzae* type b, hepatitis B, and yellow fever vaccines and vitamin A supplementation.

## Side effects

The measles vaccine may cause within 24 hours of vaccination mild pain and tenderness at the injection site. In most cases, they spontaneously resolve within two to three days without further medical attention. A mild fever can occur in 5–15% of vaccinees 7 to 12 days after vaccination and last for 1–2 days. Rash occurs in approximately 2% of recipients, usually starting 7–10 days after vaccination and lasting 2 days. The mild side effects occur less frequently after the second dose of a measles-containing vaccine and tend to occur only in persons not protected by the first dose. Encephalitis has been reported following measles vaccination at a frequency of approximately one case per million doses administered although a causal link is not proven.

## Contraindications

There are few contraindications to the administration of measles vaccine. It is particularly important to immunize children with malnutrition. Previous allergy to measles vaccine is a contraindication. Low grade fever, mild respiratory infections or diarrhoea, and other minor illnesses should not be considered as contraindications. It is contraindicated in patients with a known severe allergy to .....  
(specify the antibiotic used as a preservative). Egg allergy is not considered to be a contraindication to vaccination. Since the effect of the live measles virus vaccine on the fetus is not known, it is also contraindicated in pregnancy.

## Immune deficiency

Children with known or suspected HIV infection are at increased risk of severe measles. Such children should be offered measles vaccine as early as possible. The standard WHO recommendation for children at high risk of contracting measles is to immunize with measles vaccine at 6 months of age with a second dose at 9 months. This recommendation should be applied to children with known or suspected HIV infection. The vaccine is contraindicated in those with primary immune deficiency disease or suppressed immune response from medication, leukaemia, lymphoma or generalized malignancy.

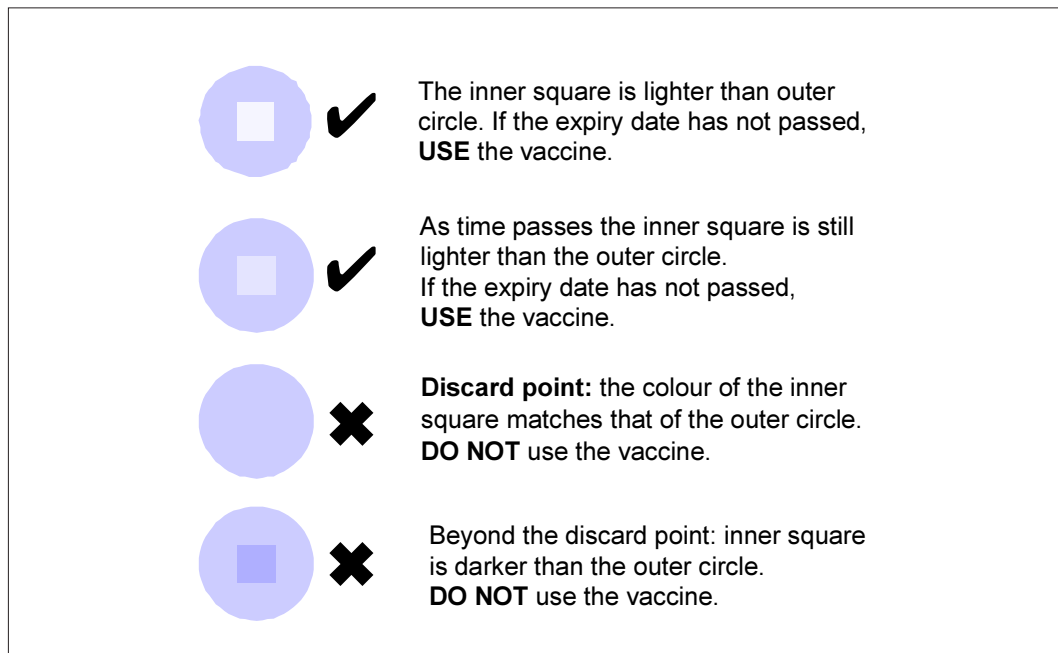
## Storage

Freeze-dried measles vaccine should be kept frozen at -20°C or in the refrigerator between +2°C and +8°C until used. The vials of vaccine and the diluent should be transported together, but the diluent must not be frozen. The vaccine should be protected from sunlight.

## Presentation

The vaccine comes in vials of ..... doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot, which appears on the label of the vial, is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## Oral polio vaccine for children

### Description

The live oral polio vaccine (OPV) is a trivalent vaccine containing suspensions of types 1, 2 and 3 attenuated poliomyelitis viruses (Sabin strains) prepared in ..... (specify cell substrate). Each dose contains ..... (specify) ..... infective units of type 1, and ..... (specify) of type 2, and ..... (specify) of type 3. .... (specify) is used as a stabilizer. OPV may contain trace amounts of ..... (specify antibiotic).

### Administration

OPV must only be administered orally. Two drops are delivered directly into the mouth from the multidose vial by dropper or dispenser. For older children it may be preferred to avoid the possible bitter taste by first placing the drops on a sugar lump or in syrup. Care should be taken not to contaminate a multidose dropper with saliva of the vaccinee.

Once opened, multi-dose vials should be kept between +2°C and +8°C.

Multi-dose vials of OPV from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the *WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water;
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure).

### Immunization schedule

Infants should receive at least three doses of OPV at minimum intervals of 4 weeks. WHO recommends the following schedule in endemic countries: Birth, 6, 10, 14 weeks. In non-endemic areas the first dose can be given from 6 weeks with the first dose of DTP.

OPV can be given safely and effectively at the same time as measles, rubella, mumps, DTP, DT, TT, Td, BCG, hepatitis B, *Haemophilus influenzae* type b, yellow fever vaccine and vitamin A supplementation.

### **Side effects**

In the vast majority of cases there are no side effects. Very rarely, there may be vaccine-associated paralysis (one case per 1 million doses administered). Persons in close contact with a recently vaccinated child may very rarely be at risk of vaccine-associated paralytic poliomyelitis.

### **Contraindications**

No adverse effects are produced by giving OPV to a sick child. In case of diarrhoea, the dose received will not be counted as part of the immunization schedule and it should be repeated after recovery.

### **Immune deficiency**

Individuals infected with human immunodeficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with OPV according to standard schedules.

However, the vaccine is contraindicated in those with primary immune deficiency disease or suppressed immune response from medication, leukaemia, lymphoma or generalized malignancy.

### **Storage**

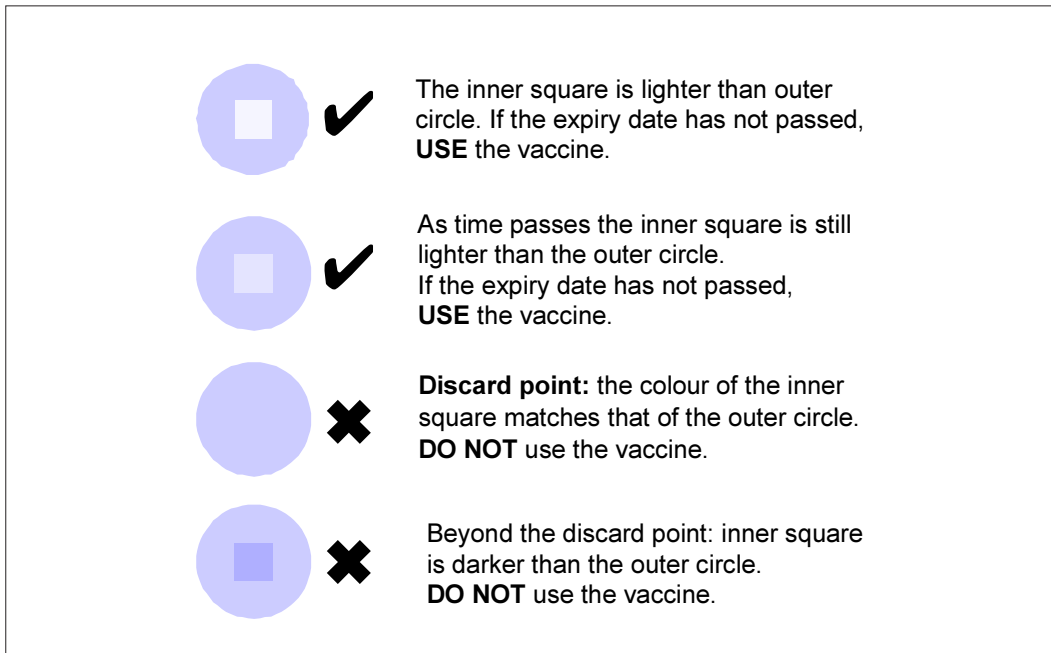
Vaccine is potent if stored at not higher than -20°C until the expiry date indicated on the vial. It can be stored for up to six months between +2°C and +8°C.

The vaccine supplied in plastic tubes may change colour due to storage with dry ice; however this does not affect the quality of the vaccine.

### **Presentation**

The vaccine comes in vials of ..... doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot, which appears on the label of the vial, is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## *Haemophilus influenzae* b vaccine (freeze-dried)

### Description

The vaccine is a bacterial subunit vaccine containing highly purified, non-infectious *Haemophilus influenzae* type b (Hib) capsular polysaccharide chemically conjugated to a protein ..... (specify) .....  
 The polysaccharide is derived from Hib bacteria grown in chemically defined media, and subsequently purified through a series of ultrafiltration steps.....  
 (specify, if appropriate) is used as a preservative (specify amount per dose).  
 The vaccine is available as a freeze-dried monovalent preparation to be diluted with diluent provided separately for that purpose. Each dose contains .....mg Hib conjugate.

### Administration

Immunization consists of a single dose of 0.5 ml injected intramuscularly into the anterolateral aspect of the thigh in infants or into the deltoid muscles of older children. A sterile needle and sterile syringe must be used for each injection. Once vaccine has been reconstituted, it should be used the same day (preferably immediately but by no means beyond six (6) hours after reconstitution), and only then if the vial has been maintained between +2°C and +8°C and protected from sunlight. Any opened container remaining at the end of a session (within six hours of reconstitution) should be discarded. The vaccine vial monitor (see figure), if present, is removed on reconstitution.

The diluent supplied is specially designed for use with this vaccine. Only this diluent may be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or for Hib vaccine from other manufacturers. Water for injection may **not** be used for this purpose. **Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine.** Diluent must not be frozen but must be cooled between +2°C and +8°C before reconstitution.

### Immunization schedule

In general, a three dose primary series is given at the same time as the primary series of DTP. The first dose is given to children at 6 weeks of age or older, and the second and third are given at 4–8 week intervals along with DTP. A three-dose primary series will be considered routine.

Hib vaccine can be given safely and effectively at the same time as BCG, DTP, measles, polio (OPV or IPV), hepatitis B and yellow fever vaccines and vitamin A supplementation. If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it is manufactured as a combined product (e.g. DTP-Hib).

## Side effects

The vaccine is very well tolerated. Localized reactions may occur within 24 hours of vaccination, when recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions, including fever, rarely occur following administration of Hib vaccines. More serious reactions are very rare; a causal relationship between more serious reactions and the vaccine has not been established.

## Contraindications

Known hypersensitivity to any component of the vaccine, or a severe reaction to a previous dose. The vaccine will not harm individuals previously infected with the Hib bacteria.

## Immune deficiency

Children infected with human immunodeficiency virus (HIV) both asymptomatic and symptomatic, should be immunized with Hib vaccine according to standard schedules.

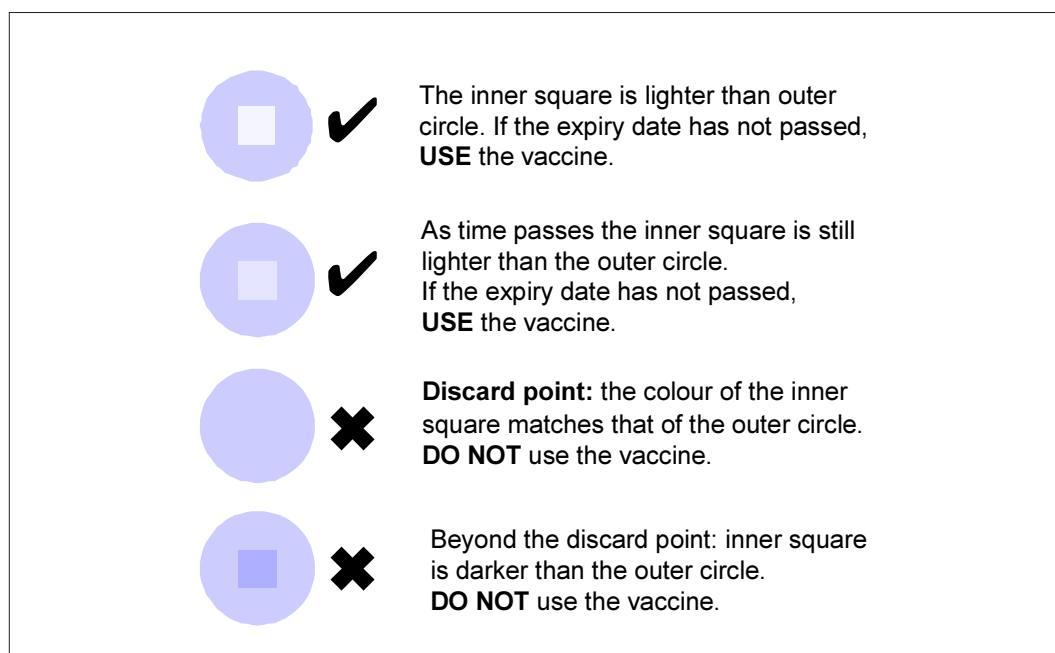
## Storage

Hib vaccine should be stored and transported between +2°C and +8°C. The diluent must not be frozen.

## Presentation

The vaccine comes in single dose vials or vials of ..... (specify) doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## *Haemophilus influenzae* b vaccine (liquid)

### Description

The vaccine is a bacterial subunit vaccine containing highly purified, non-infectious *Haemophilus influenzae* type b (Hib) capsular polysaccharide chemically conjugated to a protein ..... (specify) .....  
The polysaccharide is derived from Hib bacteria grown in chemically defined media, and subsequently purified through a series of ultrafiltration steps.....  
(specify, if appropriate) is used as a preservative (specify amount per dose).  
The vaccine is available as a freeze-dried monovalent preparation to be diluted with diluent provided separately for that purpose. Each dose contains .....mg Hib conjugate.

### Administration

The vaccine should be shaken before use. It should be injected intramuscularly into the anterolateral aspect of the thigh in infants, or into the deltoid muscles of older children or adults. One dose is 0.5ml. A sterile syringe and sterile needle should be used for each injection.

Once opened, multi-dose vials should be kept between +2°C and +8°C.

Multi-dose vials of liquid Hib from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the *WHO policy statement: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water;
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure).

### Immunization schedule

In general, a three dose primary series is given at the same time as the primary series of DTP. The first dose is given to children at 6 weeks of age or older, and the second and third are given at 4–8 week intervals along with DTP. (A three-dose primary series will be considered routine. One conjugate is licensed for a two-dose primary series, but is not marketed widely.) A booster dose is recommended in some countries, and if given, should be administered between 12 and 18 months.

Hib vaccine can be given safely and effectively at the same time as BCG, DTP, measles, polio vaccines (OPV or IPV), HepB, yellow fever vaccines and vitamin A supplementation. If Hib vaccine is given as a separate injection at the same time as other vaccines, it should be administered at a different site. It should not be mixed in the vial or syringe with any other vaccine unless it is manufactured as a combined product (e.g. DTP-Hib).

## Side effects

The vaccine is very well tolerated. Localized reactions may occur within 24 hours of vaccination, when recipients may experience pain and tenderness at the injection site. These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions, including fever, rarely occur following administration of Hib vaccines. More serious reactions are very rare; a causal relationship between more serious reactions and the vaccine has not been established.

## Contraindications

Known hypersensitivity to any component of the vaccine, or a severe reaction to a previous dose. The vaccine will not harm individuals previously infected with the Hib bacteria.

## Immune deficiency

Children infected with human immunodeficiency virus (HIV) both asymptomatic and symptomatic, should be immunized with Hib vaccine according to standard schedules.

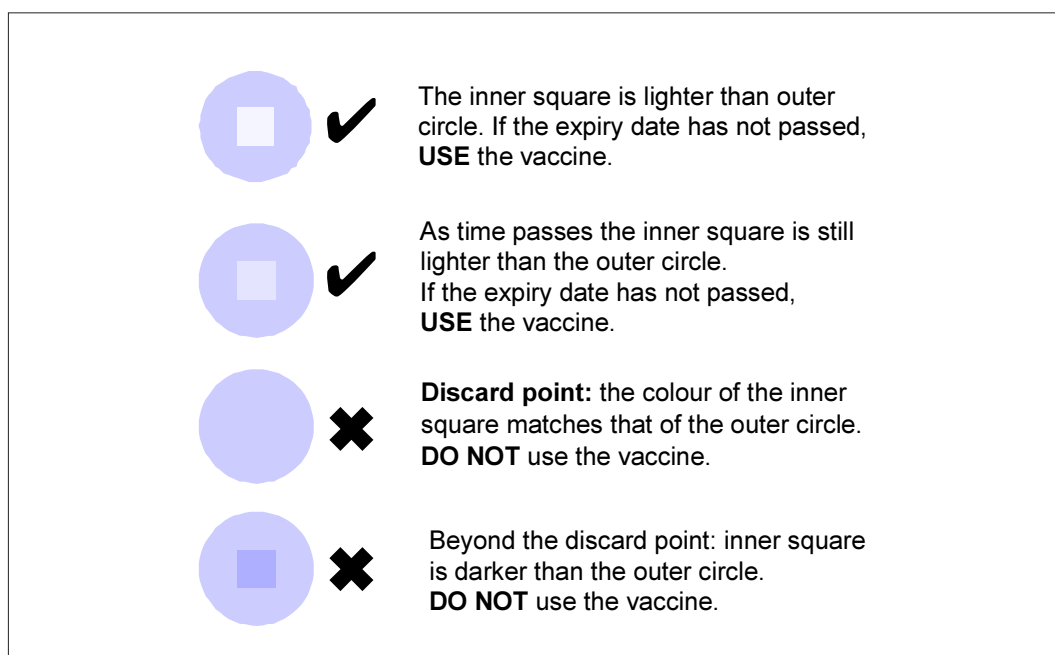
## Storage

Hib vaccine should be stored and transported between +2°C and +8°C. It must not be frozen.

## Presentation

The vaccine comes in single dose vials or vials of ..... (specify) doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## Yellow fever vaccine

### Description

An attenuated live virus vaccine containing freeze-dried attenuated virus from the 17D strain produced in eggs.

### Administration

The vaccine is for the active immunization of adults and children from the age of six months against yellow fever. A 0.5 ml dose of vaccine should be administered intramuscularly or deep subcutaneously, preferably in the upper arm. A sterile needle and sterile syringe should be used for each injection.

Because of sensitivity to ultraviolet light, the vaccine must be protected from sunlight. Once the vaccine has been reconstituted, it should be used the same day (preferably immediately but by no means beyond six hours after reconstitution), and only then if the vial has been maintained between +2°C and +8°C and protected from sunlight. If not used immediately after reconstitution, the vaccine should be kept on ice to maintain its temperature between +2°C and +8°C. Any opened container remaining at the end of a session (within six hours of reconstitution) should be discarded. The vaccine vial monitor (see figure) if present would be removed on reconstitution.

The diluent supplied by the manufacturer is specially designed for use with this vaccine. Only this diluent may be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or from other manufacturers. Water for injection may **not** be used for this purpose. **Using an incorrect diluent may result in damage to the vaccine and/or serious reactions to those receiving the vaccine.** Diluent must not be frozen but must be cooled between +2°C and +8°C before reconstitution. **The vaccine should not be reconstituted with another vaccine.**

### Immunization schedule

In countries where yellow fever poses a risk for children, the vaccine is given as soon as possible after 6 months (180 days) of age. Most countries administer yellow fever vaccine at 9 months of age at the same visit as measles vaccine. Yellow fever vaccine can also be given safely and effectively at the same visit as DT, Td, TT, BCG, polio (OPV and IPV), hepatitis B, and *Haemophilus influenzae* type b vaccines and vitamin A supplementation. A single dose of vaccine provides protection for at least 30 years, and probably for life in most recipients. When administered for purposes of the International Certificate of Vaccination, a dose of yellow fever vaccine is valid for a period of 10 years, starting 10 days after the date of immunization.

## Side effects

Reactions to yellow fever vaccine are generally mild. Some 2-5% of vaccinees have mild headaches, myalgia, low-grade fevers, or other minor symptoms 5–10 days after vaccination. Immediate hypersensitivity reactions characterized by rash, urticaria, or asthma occur in less than one in one million persons, and principally among those with a history of egg allergy. Generally, persons who can eat eggs or egg products may receive the vaccine. If vaccination of an individual with a questionable history of egg hypersensitivity is considered essential because of high risk of exposure, an intradermal test dose may be administered under close medical supervision.

Serious adverse reactions are extremely rare, with only 22 patients with encephalitis reported to WHO in over 200 million doses of 17D yellow fever vaccine given worldwide since 1945. Some rare cases of hepatic failure can occur. Since most occurred in children under 4 months of age, WHO recommends that the vaccine not be given to children under 6 months of age.

## Contraindications

For theoretical reasons, yellow fever vaccine is not routinely recommended for pregnant women; however, there is no evidence that vaccination of a pregnant woman is associated with abnormal effects on the fetus. In the outbreak setting, the risk of disease would outweigh the small theoretical risk from immunization.

## Immune deficiency

Yellow fever vaccine can be given to asymptomatic HIV-infected patients, **but should not be given to symptomatic HIV-infected persons**. This advice may be modified if the risk from yellow fever infection is greater than from the theoretical risk of the vaccine.

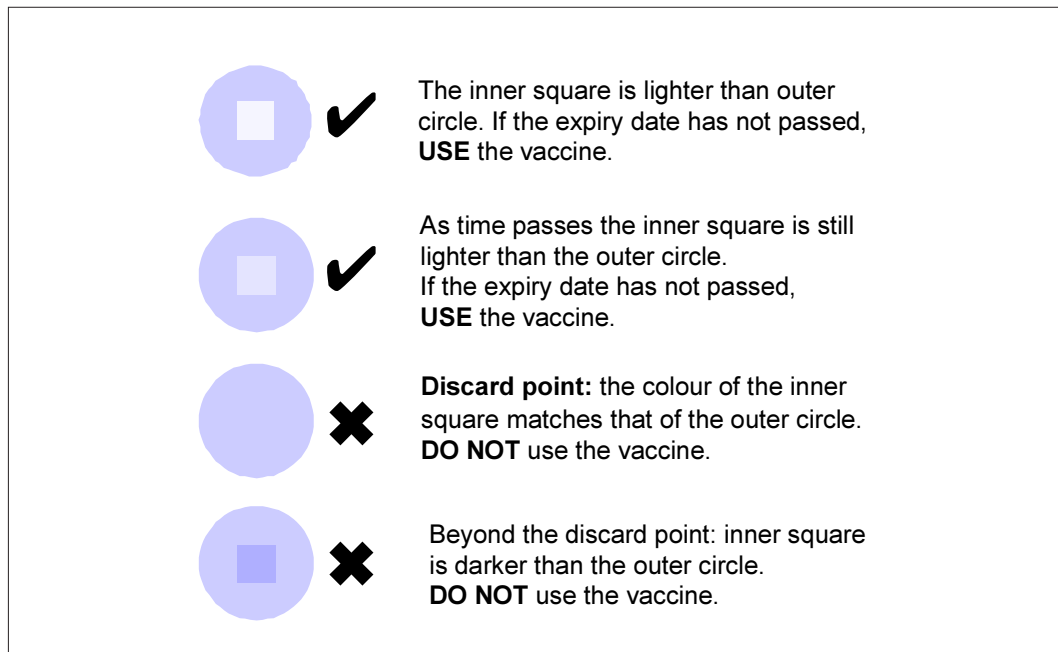
## Storage

The vaccine should be transported and stored at +2°C to +8°C. The vials of vaccine and the diluents should be stored and transported together.

## Presentation

The vaccine comes in vials of ..... doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

## Hepatitis b vaccine

### Description

The vaccine is a subunit viral vaccine containing highly purified, non-infectious particles of hepatitis B surface antigen (HBsAg), produced by DNA recombinant technology in ..... (*state which*) cells. The vaccine is adsorbed onto ..... (specify). ..... (specify) is used as a preservative (specify amount per dose). The vaccine contains ....mg HbsAg.

### Administration

The vaccine should be shaken before use. It should be injected intramuscularly into the anterolateral aspect of the thigh in infants, or into the deltoid muscles of older children or adults. One dose is 0.5ml. A sterile syringe and sterile needle should be used for each injection.

Once opened, multi-dose vials should be kept between +2°C and +8 °C.

Multi-dose vials of hepatitis B vaccine from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the *WHO: The use of opened multi-dose vials in subsequent immunization sessions*. WHO/V&B/00.09):

- the expiry date has not passed;
- the vaccines are stored under appropriate cold chain conditions;
- the vaccine vial septum has not been submerged in water;
- aseptic technique has been used to withdraw all doses;
- the vaccine vial monitor (VVM), if attached, has not reached the discard point (see figure).

### Immunization schedule

In countries where perinatal transmission of hepatitis B is common, the first dose should be given as soon as possible after birth. If perinatal transmission is uncommon, or if delivery at birth is not feasible, the first dose can be given with the first dose of DTP. The second dose should be administered one month after the first dose. The third dose should be administered one to twelve months after the second dose.

Hepatitis B vaccine can be given safely and effectively at the same time as BCG, DTP, measles, polio (OPV or IPV), *Haemophilus influenzae* type b, and yellow fever vaccines and vitamin A supplementation. If hepatitis B vaccine is given at the same time as other vaccines, it should be administered at a separate site. It should not be mixed in the vial or syringe with any other vaccine unless it is manufactured as a combined product (e.g. DTP-HepB).

## Side effects

The vaccine is very well tolerated. Some temporary swelling, tenderness and redness at the site of the injection occur in some individuals. Other minor reactions such as malaise or fever occur in less than 2% of individuals. More serious reactions are rare; a causal relationship between more serious reactions and the vaccine has not been established.

## Contraindications

Known hypersensitivity to any component of the vaccine, or a severe reaction to a previous dose. The vaccine will not harm individuals currently or previously infected with the hepatitis B virus. Individuals infected with human immunodeficiency virus (HIV) both asymptomatic and symptomatic, should be immunized with hepatitis B vaccine according to standard schedules.

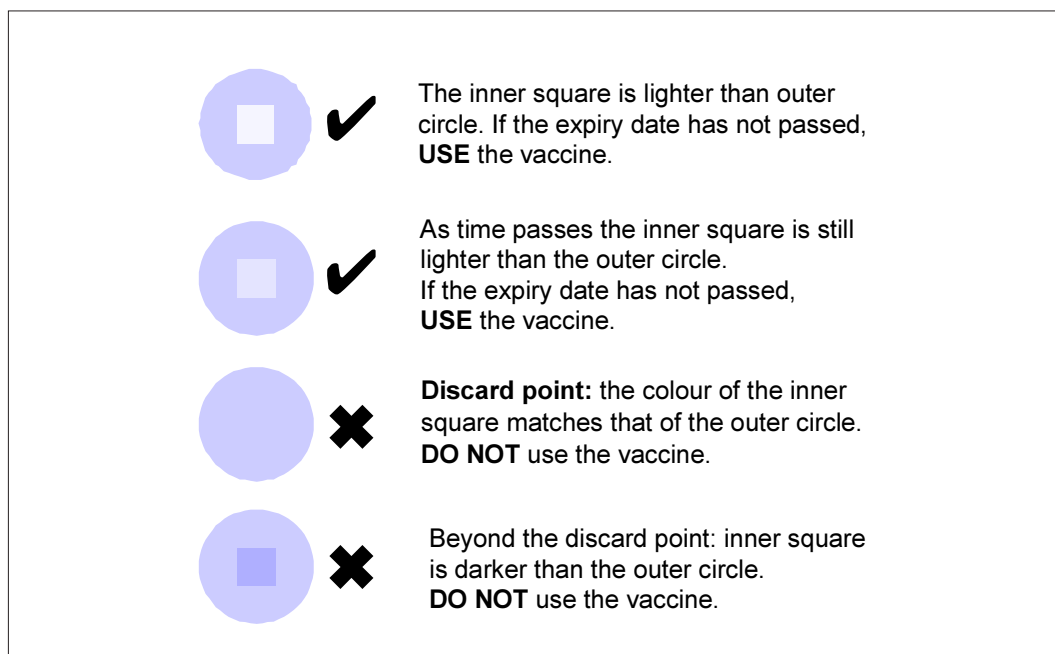
## Storage

Hepatitis B vaccine should be stored and transported between +2°C and +8°C. **It must not be frozen.**

## Presentation

The vaccine comes in single dose vials or vials of ..... (specify) doses.

Figure: The vaccine vial monitor



Vaccine vial monitors (VVMs) are part of the label on ..... (specify vaccine) supplied through ..... (specify supplier or manufacturer). The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

# Quality of the cold chain

## WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services

- 1 At any time in the process of distribution and at the time a vaccine is administered the vaccine vial monitor (VVM) indicates whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates to health workers whether a vaccine can be used.
- 2 The VVM enables failures in the cold chain to be highlighted in a simple, unambiguous manner and focuses managers' attention and resources on the weakest links in the chain. It is therefore a tool for ensuring the quality of the cold chain at the lowest possible cost.
- 3 VVMs have been in use with oral polio vaccine (OPV) since 1996. If adequate training is provided they are well accepted by health workers and managers. They have contributed to the success of national immunization days, particularly in areas with a weak cold-chain infrastructure, and they clearly help to reduce vaccine wastage.
- 4 Agencies purchasing vaccines should request manufacturers to supply all vaccines with VVMs that meet WHO specifications.
- 5 All users of vaccines with VVMs should monitor the wastage of vaccine resulting from the VVM indication of a cold-chain failure; all managers of immunization services should evaluate these wastage statistics and strengthen the cold chain accordingly.



This policy statement is issued jointly by the World Health Organization, Geneva, Switzerland, and the United Nations Children's Fund (UNICEF Programme Division, New York, USA, and UNICEF Supply Division, Copenhagen, Denmark).



## Background

During the first 21 years of the Expanded Programme on Immunization, from 1974 to January 1996, there were no means for the health worker to know whether a vial of vaccine had been exposed to a combination of excessive heat over time and whether it was, therefore, no longer potent. To compensate for this the vaccine cold-chain infrastructure was overspecified: excessively high standards required costly refrigeration equipment and fastidious management regulations. These standards have, to some extent, achieved their purpose, but the new technology is superior in giving a direct indication of the potency of each vaccine vial and permitting huge savings in the cost of immunization services.

Between 1981 and 1992, VVMs were tested in 19 countries. Interviews and focus group discussions were held with over 170 health workers to obtain feedback on VVM design, use, and preliminary training materials. During in-depth field studies, 89 700 VVMs were used on vaccine vials distributed to 1432 health centres. Since January 1996, OPV vials supplied by UNICEF have been systematically fitted with VVMs. The correlation between the VVM indication and the potency of polio vaccine was tested independently in 1997 by Dr David Wood of the National Institute of Biological Standards and Control, London. In 1999 the Consumer Association Laboratories in the United Kingdom tested the performance of these VVMs by standard procedures<sup>1</sup> and confirmed that they met WHO performance specifications<sup>2</sup>.

The impact of VVMs on field operations, both routine and supplemental, has been assessed in Bhutan, Ghana, Kenya, Nepal, Sudan, Tanzania, Turkey, and Viet Nam. The studies show that polio vaccine may be taken successfully beyond the reach of the cold-chain infrastructure during national immunization days in remote areas and that vaccine wastage rates are reduced. They also show that the VVM detects areas where the cold chain is weak and focuses measures to strengthen the cold chain in those areas where reinforcement is needed. Finally, until VVMs are available for all vaccines there is a clear danger that vaccines with VVMs will be used as a proxy for vaccines without VVMs. The results of the evaluations were presented and discussed at the 1998 meeting of the Technical Network for Logistics in Health (TECHNET), which issued the following statement:

**VVMs on vials of OPV are a valuable addition to immunization services, enabling health workers to decide whether a vaccine should be used. TECHNET recommends that appropriate VVMs for all vaccines be introduced as soon as possible.**

VVMs are now available for all vaccines.

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<sup>1</sup> See WHO standard test procedure for vaccine vial monitors for polio vaccine, reference E6/PROC/5, included in the document *Equipment performance specifications and test procedures* (WHO/EPI/LHIS/97.09).

<sup>2</sup> See WHO standard performance specification for vaccine vial monitors for oral polio vaccine, reference E6/IN.5, included in the document *Equipment performance specifications and test procedures* (WHO/EPI/LHIS/97.09).

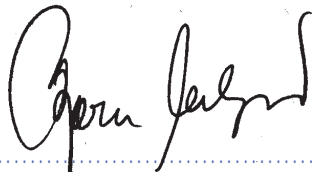
## Costs

Despite the extensive operational benefits of VVMs, their use does not increase system costs. Indeed, there is a net saving to immunization programmes when VVMs are used. For example, when the results of a study in 12 provinces of Turkey were extrapolated nationally, the countrywide savings from wastage reduction during national immunization days for polio eradication amounted to about US\$ 71 500 per year. Again, when a study of eight districts in Bhutan was extrapolated to the national consumption of polio vaccine for routine immunization the annual saving was about \$6770.

Such savings in the cost of immunization arise from reductions in the wastage of vaccine that is rejected due to cold-chain failures, in the wastage of partly-used vials of vaccine taken to the field, and in the cost of cold-chain equipment where the climate is temperate.

If similar reductions can be achieved in typical rates of wastage when VVMs are used with all the liquid vaccines figuring in routine immunization programmes the gross savings due to the introduction of VVMs could reach \$4.8 million annually.

**Consequently, when vaccine wastage is included in the system cost of using VVMs it can be expected that there will be no increase in vaccine costs to country programmes and that there could be significant global savings.**



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This document is available on the Internet at:  
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